THEORETICAL STUDIES ON GENETIC LIMITS TO NATURAL AND ARTIFICIAL SELECTION WITH MUTATION

By

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I DEDICATE THIS THESIS TO MY WIFE MA JIA.

I declare that this thesis is my composition and that the research described in it is my own work.

But science, no less than theology or philosophy, is the field for personal influence, for the creation of enthusiasm, and for the establishment of ideals of self-discipline and self-development. No man becomes great in science from the mere forces of intellect, unguided and unaccompanied by what really amount to moral forces. Behind the intellectual capacity there is the devotion to truth, the deep sympathy with nature, and the determination to sacrifice all minor matters to one great end.

——— Karl Pearson

(On the first page of the Memoir of his friend and colleague, W. F. R. Weldon)

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SUMMARY

Theoretical studies have been made of the interplay between natural and artificial selection in the context of the discussion of long-term response and selection limit in populations of infinite size. Natural selection is assumed to act on the phenotype of a quantitative character in a Gaussian form towards an optimum value (stabilizing selection) and artificial selection is by truncation. With the assumption of a normal phenotypic distribution it was found that the population approaches a selection limit, determined by the intensities of stabilizing and truncation selection and the phenotypic variance, at a rate which is a function of the intensity of stabilizing selection and heritability. The maintenance of genetic variance at the selection limit has been examined in terms of mutation-selection balance. It was found that truncation selection can substantially reduce the equilibrium genetic variance below that when only stabilizing selection is acting.

A general procedure for analysing the change of genotypic distribution under the long-term stabilizing and truncation selection has been developed in a distribution expansion —— the Gram-Charlier expansion —— in the bivariate case to test the robustness of the Gaussian distribution assumption. It was observed that long-term truncation introduces departures from normality mainly through gene frequency change, rather than through the generation of linkage disequilibrium. For reasonable choices of parameters, the Gaussian approximation to the genotypic distribution performs reasonably well for predicting the response even up to the selection limit.

The analysis of the interplay between stabilizing and directional selection has been extended to multiple characters in the context of the discussion of adaptation and coadaptation of quantitative characters in evolution. An interesting result emerged from the analysis that the correlated responses to selection in the long term differ qualitatively from those in the short term. Whereas in the short term the correlated responses depend on genetic correlations between characters, in the long term they are determined by the "coadaptive coefficients", the parameters of the stabilizing selection function. Based on this result, it was argued that the major cause for the coadaptation between quantitative characters in evolution might be the correlated stabilizing selection, not genetic correlations, and it was also suggested that the main origin of interpopulation correlations between quantitative characters might be the "coadaptive coefficients", not genetic correlations.

CHAPTER 1

INTRODUCTION

1.1. Understanding of selection limit

Selection experiments have progressed from the original purposes of determining whether selection would be effective and establishing whether the selection response could be predicted for the short term to more complicated and complex objectives, for example assessing the importance of correlated responses to long-term selection and determining characteristics of selection limits, such as total response expected, duration of response, and parameters of the plateaued population.

The selection limit or plateau is one of the most interesting phenomena of the selection process and also one of the most interesting problems of quantitative genetics. It is of interest from the practical standpoint because it is a problem that some selected lines of farm animals (*e.g.* poultry) are or are going to be facing, from the experimental standpoint because of the information it may yield regarding the genetic structure of populations and from the theoretical standpoint because it is a way to interpret experimental results and to elaborate the evolving process of quantitative characters.

The theoretical understanding of long-term response and selection limit began with Robertson's (1960) theory, in which some theoretical concepts of selection limit were proposed, such as total response,

half-life response and ratio of total response to initial response. The theory was based on the interpretation that, if all the favourable genes were fixed in a population, there would be no further response to selection. In a small population, these favourable genes may be lost by chance. The smaller the population, the greater will this chance be, so the total response is a function of the effective population size and also the intensity of selection.

As stated by Robertson (1960), it may of course happen that a population will reach a selection limit while still retaining genetic variance. This could be brought about by a conflict between natural and artificial selection, since natural selection is usually thought to favour intermediate expressions of quantitative characters, while artificial selection is for extremes.

Two models have been proposed for the action of natural selection on quantitative characters. One is stabilizing (also known as centripetal, normalizing or optimum) selection, another is overdominant selection. Stabilizing selection has received considerable attention over the last several decades (*e.g.*, Fisher, 1930; Wright, 1935; Haldane, 1954; Robertson, 1956; Latter, 1970; Lande, 1975). In this selection model, the fitness of an individual is assumed to be a function of its phenotypic deviation from an intermediate optimum. In overdominant selection, on the other hand, it is assumed that heterozygotes at the loci affecting the quantitative character have higher fitness, and this has been thought by many people to be important as a possible explanation for the maintenance of genetic variability in both natural and artificial

populations (*e.g.*, Lerner, 1950, 1954; Robertson, 1956; Bulmer, 1973; Gillespie, 1984).

The conflict between stabilizing and truncation selection has been considered by James (1962) in the context of the selection limit. He found the amount by which the population mean can be increased by artificial selection against counter-balancing natural selection, but was unable to determine the extent of genetic variation maintained in the population at the selection limit. In contrast, Nicholas and Robertson (1980) investigated another model called the homeostatic model where the conflict is between overdominant and directional selection. The model actually assumed that, if natural selection for heterozygotes were strong enough against directional selection for a homozygote, the alleles would remain segregating in the population. Their analysis is interesting because it provided a possible reason for the cessation of response long before complete homozygosity. However, in all these studies, mutation as a source of introducing fresh variability has been ignored.

1.2. The role of mutation

There has been a great advance in recent years in quantitative genetics through the understanding of the role of mutation in the maintenance of genetic variability in natural populations and in the long-term response to artificial selection. This was represented by the two branches of theoretical analyses. One is on the mutation and natural selection balance and the other is on the mutation and population size interaction.

It is a fundamental observation that most quantitative characters in most populations exhibit considerable genetic variation. It was not until Lande (1975) who, based on a mathematical analysis and empirical estimates of the relevant parameters, argued that mutation can maintain the genetic variance in the face of stabilizing selection, that this mutation-selection hypothesis, discussed earlier by Latter (1960), Kimura (1965) and Bulmer (1972), attracted considerable attention among geneticists. This attention was further enhanced by a substantial review and analysis made by Turelli (1984) in the argument. Several points were cleared up by Lande (1975) and Turelli (1984): (i) If the total mutation rate of the loci controlling the character concerned is around 0.01 and the intensity of stabilizing selection (ω^2/σ_e^2, see below) is about 10-20, which seem to be supported by the relevant data, both Lande's and Turelli's analyses predict large levels of genetic variability at equilibrium. (ii) The different predictions of equilibrium genetic variances between Kimura's (1965) and Lande's (1975) analyses and Latter's (1960) and Bulmer's (1972) analyses are not due to the number of alleles assumed but to the use of different mathematical approximations with different underlying assumptions about the relative magnitudes of parameters involved. (iii) The amount of expressed genetic variation maintained by mutation does not seem to be dependent on the arrangement of the loci in the genome. Among the various assumptions made in the above analyses, one is that selection acts on a single character, and thus the pleiotropic effects of mutants which subject to multivariate selection are ignored. It has been shown that, if the pleiotropic effects of mutants under multivariate stabilizing selection are considered, the univariate

prediction of equilibrium genetic variance tends to be biased upward (Turelli, 1985), because the force of selection on a single character can greatly be strengthened by selection on other phenotypically correlated characters (Lande and Arnold, 1983). Alternatively, Gillespie (1984) has shown that, if pleiotropic effects involve balancing selection rather than phenotypic stabilizing selection, pleiotropy can be a potent force maintaining genetic variance.

Mutation has usually been ignored in the study of long-term response to artificial selection, because it has been a common view that the time scale was too short and population sizes too small in artificial selection experiments or breeding programmes for new mutations to make a considerable contribution to selection response. There are, however, several long term selection experiments which demonstrated that response to directional selection may continue for 50 to 100 generations before there is any indication that a plateau is being approached (Dudley, 1977; Enfield, 1980; Yoo, 1980a). For this duration, mutation in the broad sense occurring during the experiments from whatever sources should be capable of making a substantial contribution to long-term responses (Frankham, 1980; Hill, 1982b). Additional evidence, including estimation of new variance from mutation in selection experiments (Hill, 1982b; Enfield, 1986), high incidences of visible mutants discovered long after initiation of selection experiments (Hollingdale, 1977; Yoo, 1980b) and wave response patterns obtained in several experiments (Mather and Harrison, 1949; Thoday, Gibson and Spickett, 1964; Lopez-Fanjul and Hill, 1973), further indicated the possible role of mutation in the long-term responses. In a series of studies, Hill

(1982a, 1982b, 1985, 1986) has evaluated the importance new mutations might play in supplying useful variation for continuing response to selection and the effect of interaction between population size and mutation in the long-term response and the variation of response from new mutations.

1.3. Interpretation of long-term correlated responses

Recent advance in quantitative genetics also includes the applications of quantitative genetic concepts and methods in understanding some evolutionary problems. Among the problems attacked, one is how to detect and explain the correlated responses to selection in the wild. This problem has been attempted by Lande. He used the concept of genetic correlations to discuss the measurement of selection forces on correlated characters (Lande and Arnold, 1983) and the problem of allometry (correlations in the development of phenotypic characters) with regard to character similarity between species in time or across taxonomic units (Lande, 1979). Lande's approach seems quite reasonable, but there is some problem in it. In this thesis (chapter 5), I shall reexamine the basic principle in Lande's analyses that the correlated responses to selection are caused by genetic correlations between characters in the long term.

1.4. Matters to be considered

Some questions about long-term response and selection limit have been attempted and may partly have been answered, but more have

arisen. From a strictly theoretical point of view, many questions associated with long-term response and selection limit are still remaining far from being solved, such as how far a selection experiment can go, what are the mechanisms for maintenance of genetic variability at a limit to selection, whether the genotypic distribution can still remain approximately normal at the selection limit and what is the long-term consequence of selection on correlated characters? In view of the importance of these questions in the interpretation of results from long-term selection experiments and in our understanding of evolution of quantitative characters, it is desirable to make an effort in finding a better understanding of the questions.

It is the purpose of this thesis to discuss some aspects of these questions through analysing the interaction between stabilizing and directional selection. In chapter 2, I shall present a phenotypic analysis of the change of selection differential under stabilizing and truncation selection, which will serve as an introduction to the long-term response pattern associated with this selection model. Chapter 3 will be devoted to the discussion of maintenance of genetic variation at the limit to selection in terms of mutation-selection balance. An effort will be made to test the robustness of the assumption of normal distributions of genotypes and phenotypes in the long-term process of selection in chapter 4. In this chapter, I shall also try to clarify some concepts of selection limit and discuss some aspects of the effects of mutation on long-term responses. Chapter 5 is an extension of the analyses of previous chapters from single character selection to multiple character

selection. Particular attention will be given to long-term correlated responses to selection. Because the result has implications to some evolutionary problems, the argument in this chapter will centre on the question: what is the major cause for the coadaptation between quantitative characters in evolution? In the last chapter (chapter 6), I shall bring different analyses together to discuss their implications and draw conclusions.

CHAPTER 2

LONG TERM RESPONSE AND LIMIT TO STABILIZING AND TRUNCATION SELECTION

2.1. Introduction

In artificial selection experiments and breeding programmes, there may be a conflict between artificial and natural selection. Usually, the aim of artificial selection is to improve some particular characters and thus is generally directed towards extreme phenotypic values. It is observed that natural selection often favours intermediate expression of metric characters unless these characters are very closely associated with fitness (*e.g.*, Linney, Barnes and Kearsey, 1971). So plateaux obtained in artificial selection experiments could result from the opposing forces of directional and natural selection rather than from a loss of additive genetic variance, as indicated by some long-term selection experiments (*e.g.*, Lerner and Dempster, 1951; Clayton and Robertson, 1957; Latter, 1966; Roberts, 1966; Wilson *et al.*, 1971; Yoo, Nicholas and Rathie, 1980).

Based on this idea, James (1962) first analysed the selection limit under the conflict between natural and artificial selection. The form of natural selection formulated in his study is of stabilizing, which emphasizes the average phenotype and selects against either extreme phenotypes. This is based on the observations that in natural populations the most fit individuals are usually those with intermediate values on some quantitative characters (*e.g.*, Bumpus, 1899; Weldon, 1901). If this type of selection operates in

natural populations, it should operate in laboratory populations and farm animals as well. With the assumption that heritability is not greatly altered during the course of selection, James was able to develop an approximate expression for the selection limit (i.e., the maximum response to selection) which is expressed in terms of ι, the intensity of truncation selection, ω^2, a measure of the intensity of stabilizing selection and σ^2, the phenotypic variance of character.

In this chapter, I present an analysis of selection differential under the joint action of stabilizing and truncation selection. The analysis is based on the assumption that in each generation the phenotypic distribution is normal before selection. The validity of this assumption will be examined in chapter 4. Then, with the assumption that genetic variance can be maintained in the population at the selection limit (examined in chapter 3), a simple expression of the selection limit is obtained, which resembles in form as James's formula. This chapter mainly serves as an introduction to the response pattern under the conflict between stabilizing and truncation selection.

2.2. Analysis

Consider a metric character having phenotypic value x with the following probability density function among juveniles (before the operation of selection) in generation t

$$f(x)=(2\pi\sigma^2)^{-1/2}\exp\{-(x-u_t)^2/(2\sigma^2)\}, \qquad (2.1)$$

where σ^2 is the phenotypic variance which is assumed to be independent of the mean u_t. The fitness of individuals under

stabilizing selection with phenotypic value x is assumed to decrease with deviation from the optimum value according to the relation

$$w_1(x)=\exp\{-x^2/(2\omega^2)\}, \tag{2.2}$$

where the optimum value of x is taken to be zero, and ω^2 is a measure of intensity of stabilizing selection, being less intense the larger ω^2 in relation to σ^2. Stabilizing selection may act on individuals through the whole life cycle, by differential viability or reproductivity, or both. But here, for convenience, it will be assumed that the stabilizing selection occurs before truncation selection. Then it is readily shown that among the survivors after stabilizing selection, the phenotypic distribution becomes

$$\begin{aligned} f'(x) &= f(x)w_1(x)/\int f(x)w_1(x)dx \\ &= (2\pi c\sigma^2)^{-1/2}\exp\{-(x-cu_t)^2/(2c\sigma^2)\}, \end{aligned} \tag{2.3}$$

where $c=\omega^2/(\sigma^2+\omega^2)$, called the coefficient of centripetal selection by Latter (1970). The distribution (2.3) is still normal with mean $u_t'=cu_t$ and variance $\sigma'^2=c\sigma^2$.

Throughout this thesis, the superscript $'$ denotes after stabilizing selection but before truncation selection and the superscript * denotes after truncation selection.

Truncation selection induces the fitness function

$$w_2(x)=\begin{cases} 1 & \text{if } x > \tau \\ 0 & \text{otherwise,} \end{cases} \tag{2.4}$$

where τ is the truncation point in absolute value. Using (2.3) and (2.4), we can then obtain the proportion of individuals surviving the two kind of selection (mean fitness of population):

$$\bar{W}=\int f(x)w_1(x)w_2(x)dx$$
$$=P[\omega^2/(\sigma^2+\omega^2)]^{1/2}exp\{-u_t{}^2/[2(\sigma^2+\omega^2)]\}, \qquad (2.5)$$

where $P=\int_T^\infty f'(x)dx$ is the proportion of individuals surviving stabilizing selection which are then selected by truncation selection. The change in the population mean by truncation after stabilizing selection is

$$s_t{}^*=u_t{}^*-u_t'$$
$$=(1/\bar{W})\int(x-u_t')f'(x)w_2(x)dx$$
$$=\iota\omega\sigma/(\sigma^2+\omega^2)^{1/2}, \qquad (2.6)$$

where ι is the standardized selection differential of truncation selection, corresponding to P. Then the total selection differential is given by

$$s_t=u_t{}^*-u_t$$
$$=(u_t{}^*-u_t')+(u_t'-u_t)$$
$$=\iota\omega\sigma/(\sigma^2+\omega^2)^{1/2}-u_t\sigma^2/(\sigma^2+\omega^2). \qquad (2.7)$$

This relation would hold for every generation if the phenotypic distribution remained normal before selection and σ^2 were constant. When the second assumption is violated, σ^2 has to be replaced by $\sigma_t{}^2$ in (2.7).

The change in the average phenotypic value in response to selection must equal the product of heritability and selection differential, *i.e.*,

$$\Delta u_t=u_{t+1}-u_t$$
$$=s_t h_t{}^2, \qquad (2.8)$$

where $h_t{}^2$ is the heritability of the character at generation t. Thus

at a selection limit, where $\Delta u=0$, either s or h^2 should be zero. This analysis is a little different from the traditional concept (*e.g.*, Falconer, 1981). Usually the response to selection is regarded as the product of selection differential of truncation selection and realized heritability. When the population fails to show a response to selection, it is customary to attribute it to the loss of realized heritability, because the observed selection differential is not zero. The quantity measured is $(u_t^*-u_t')$, not $(u_t^*-u_t)$. Here u_t is supposed to be the mean phenotype of population before truncation selection, assuming there is not stabilizing selection. In the presence of stabilizing selection, the population mean shifts from u_t to u_t' before truncation by an amount which removes the response to selection in the last generation. Then, the realized heritability h_r^2 in this sense should be

$$h_r^2=\{1-\frac{\sigma u_t}{\iota\omega(\sigma^2+\omega^2)^{1/2}}\}h^2, \qquad (2.9)$$

which, when it becomes zero, does not necessarily imply that h^2 is zero.

If a limit is attained due to the attenuation of selection differential, the total predicted selection advance can be obtained by setting $s=0$ in (2.7) and is

$$u_\infty=\iota\omega(\sigma^2+\omega^2)^{1/2}/\sigma \qquad (2.10a)$$

or $$u_\infty=\iota\omega(\sigma^2+\omega^2)^{1/2}/\sigma-u_0 \qquad (2.10b)$$

if $u_0 \neq 0$. This relation was first obtined by James (1962) by a different derivation.

Furthermore, from (2.7) and (2.8), we can get

$$u_{t+1} = (1 - \frac{h^2\sigma^2}{\sigma^2+\omega^2})u_t + \frac{h^2 \iota\omega\sigma}{(\sigma^2+\omega^2)^{1/2}}. \qquad (2.11)$$

The first term on the right side of (2.11) shows the effect of stabilizing selection on the phenotypic change which is the same as Eq.14 of Lande (1975). The second is the effect of truncation selection which could be constant in standard units, if the indicated assumptions hold: *i.e.*, the phenotypic distribution is always normal before selection, h^2 and σ^2 do not change very much during the course of experiment, and the same proportion of individuals is selected by truncation in every generation. If $u_0 = 0$, the selection response in the first generation of selection may be expressed as

$$u_1 = h^2 \iota\sigma\omega/(\sigma^2+\omega^2)^{1/2}, \qquad (2.12)$$

and the ratio of the total response over the response in the first generation becomes

$$u_\infty/u_1 = (\sigma^2+\omega^2)/(\sigma^2 h^2). \qquad (2.13)$$

Finally, letting $(1 - h^2\sigma^2/(\sigma^2+\omega^2)) \approx exp\{-h^2\sigma^2/(\sigma^2+\omega^2)\}$, we find from (2.11)

$$u_t = u_0 exp\{-\frac{h^2\sigma^2 t}{\sigma^2+\omega^2}\} + [1 - exp\{-\frac{h^2\sigma^2 t}{\sigma^2+\omega^2}\}] \frac{\iota\omega(\sigma^2+\omega^2)^{1/2}}{\sigma}. \qquad (2.14)$$

Then we can get the "half-life" of the selection process, the number of generation taken to go half way to the limit (Robertson, 1960). This is

$$t_{0.5} = ln2(\sigma^2+\omega^2)/(\sigma^2 h^2) \quad \text{generations}. \qquad (2.15)$$

2.3. Discussion

There are several notable features in this analysis. First, as indicated in (2.14), the response curve is exponential, which is similar to that predicted by Robertson's (1960) theory for finite populations with directional selection alone. In this analysis the response rate, $h^2\sigma^2/(\sigma^2+\omega^2)$, is a function of h^2 and ω^2/σ^2. Therefore the half-life is expected to be longer if selection is on a character with a lower heritability and/or less intense stabilizing selection (*i.e.*, higher value of ω^2/σ^2) (2.15). Second, although the response rate is a function of heritability, the selection limit predicted is independent of heritability. Third, in a large population, the total response is maximized by having the smallest possible P (2.10), but, in a small population, P should be 0.5 to obtain the largest total response (Robertson, 1960).

A key parameter associated with this analysis is the intensity of stabilizing selection ω^2. Usually, the value of ω^2 is estimated by assaying the reduction in phenotypic variance between two stages in the life cycle with the assumptions: (i) the distribution of phenotypes is normal before selection (2.1), (ii) phenotypic fitness follow the Gaussian function (2.2), (iii) the population mean is at the optimum value, and (iv) phenotypes are scored before and after selection. There are, however, many problems associated with this kind of estimation (Turelli, 1984), among which is the multivariate action of stabilizing selection (see chapter 5). Stabilizing selection tends to act on many characters jointly. The indirect effects of stabilizing selection on every other correlated characters

will reduce the variance of the character concerned, regardless of the signs of the correlations. This would then be confounded with the "intrinsic" effect of selection on the character studied and the intensity will be overestimated from observed changes in phenotypic variance (Lande and Arnold, 1983). Thus estimates from observed reduction of variance are necessarily restricted to the "realized" intensity of selection which contains all other indirect selection effects on this character. Using the above method, Johnson (1976) summarized 15 estimates of ω^2/σ^2 from various sources, some of which gave nonsensical negative values produced by departure from the assumptions above. Ignoring the five lowest estimates, the rest ranged from 2.18 to 20 with means and median 4.03 and 3.43 respectively.

James (1962) also attempted to estimate ω^2/σ^2 from results of long-term selection experiments on *Drosophila* and poultry. The statistic he used is the ratio of total response to initial response (2.13). But he integrated (2.13) with Robertson's (1960) theory, so the effective population size N_e was inserted into the formula. From the data of fourteen selected lines in *Drosophila* and one line of poultry, he observed that ω^2/σ^2 ranged from about 5 to 10 in those cases. The lack of reliability of these and above estimates is obvious. This is not only because the final limits in many of those lines may not have been reached yet, but also the parameters involved may be poorly estimated, and moreover the assumptions required are too restrictive to hold in real situations. Despite estimation problems, these estimates, nevertheless, indicate the possible range of ω^2/σ^2 5 ~ 15 which will be used in chapters 3, 4 and 5 for

simulations.

2.4. Summary

1. Various aspects of the process of long-term response and limit to stabilizing and truncation selection have been explored in this chapter on the assumptions of normal phenotypic distribution and constant values of σ^2 *and* h^2.

2. The selection limit (*i.e.*, the maximum response) is found to be $\iota\omega(\sigma^2+\omega^2)^{1/2}/\sigma$, a function of ι, the intensity of truncation selection, ω^2, a measure of the intensity of stabilizing selection and σ^2, the phenotypic variance of character.

3. A relation between the realized heritability (h_r^2) and heritability (h^2) is formulated, which depends on the mean deviation of population from the optimum value, as well as ι, ω^2 and σ^2.

4. The response curve is found to be exponential with the response rate $h^2\omega^2/(\sigma^2+\omega^2)$, a function of h^2 and ω^2/σ^2, which is also the ratio of initial response to total response (2.13). In a finite population the response rate would also be a function of effective population size (N_e) (Robertson, 1960). If the value of h^2 remains roughly constant during the whole course of selection, this ratio is a good statistic for estimating the parameter of ω^2/σ^2, as James (1962) did.

CHAPTER 3

MAINTENANCE OF GENETIC VARIABILITY AT THE LIMIT TO SELECTION

3.1. Introduction

In the last chapter I considered the formulation of long-term response and limit to stabilizing and truncation selection on the assumption that genetic variance can be maintained in the population. This assumption will be investigated in this chapter in terms of mutation-selection balance.

The dynamics and maintenance of genetic variability of quantitative character under stabilizing selection and mutation have been studied intensively by many authors (Latter, 1960; Kimura, 1965; Bulmer, 1972, 1980; Lande, 1975; Fleming, 1979; Turelli, 1984). They examined the balance between mutation and stabilizing selection to see whether this balance could account for the high levels of heritable variation observed for many quantitative characters in natural populations. Lande (1975), in particular, has forcefully argued that high heritabilities could be maintained by this mutation-selection balance even with strong stabilizing selection. Recently, Turelli (1984) has critically reviewed this argument and numerically given the domains of applicability of the various approximations produced by him and other authors. Based on a Lerch's zeta function and numerical work, Turelli argued that the approximation he used would give a better estimate of the equilibrium genetic variance when the mutation rate per locus is of the order of

10^{-4} or less.

In the following analysis, Turelli's (1984) approximation will be used and extended to include truncation selection. A brief description of the approximation will be given first. Then follows a detail analysis of allelic frequency distribution at the limit to stabilizing and truncation selection.

3.2. The model

Consider a randomly mating diploid population of infinite size and a quantitative character which is affected by n additive loci and an independent environmental effect. At each locus it is assumed that there is potentially an infinite number of allelic states and the phenotypic effects of these alleles are continuously distributed.

Let x denote the phenotype of this quantitative character with

$$x = y + e \tag{3.1}$$

and

$$y = \sum_{i=1}^{n} (z_i^m + z_i^p), \tag{3.2}$$

where z_i^m (z_i^p) is the allelic effect of the maternally (paternally) inherited gene at the ith locus in an individual, and e is the environmental effect, assumed to be normally distributed with mean zero and variance σ_e^2.

The object is to find an approximation for the equilibrium

distribution of z_i at the limit to selection. First some other assumptions need to be made. Usually, it is assumed that the phenotypic effects of mutant alleles from a given allele state are normally distributed around the phenotypic effect of the original allele (e.g., Kimura, 1965). Then, if $f_t(z_i)$ denotes the distribution of allelic effects among gametes in generation t and mutation is assumed to occur during gametogenesis which follows selection, $f_{t+1}(z_i)$ will be

$$f_{t+1}(z_i)=(1-\mu_i)f_t'(z_i)+\mu_i\int f_t'(v_i)g(z_i-v_i)dv_i, \tag{3.3}$$

in which μ_i is the mutation rate of the ith haploid locus,

$$f_t'(z_i)=w(z_i)f_t(z_i)/\int w(v_i)f_t(v_i)dv_i \tag{3.4}$$

is the density function of allelic effects after selection, where $w(z_i)$ is the selection function on z_i, and

$$g(z_i)=(2\pi m_i^2)^{-1/2}exp\{-z_i^2/(2m_i^2)\} \tag{3.5}$$

is the density function of mutant effects, where m_i^2 is the variance of mutant effects for the ith haploid locus. Interpreting (3.3) in words: at the beginning of generation $t+1$ an allele z_i has probability $1-\mu_i$ of coming from allele z_i in the previous generation, having survived selection and without mutation, and probability μ_i of coming from another allele in the previous generation, having survived selection and mutated to z_i.

Generally speaking, it is difficult to analyse (3.3) directly without some simplification. Here we simplify (3.3) in the following way. By expanding $g(z_i-v_i)$ in Taylor's series about (z_i-u_i'), where $u_i'=\int v_i f_t'(v_i)dv_i$, we have

$$\mu_i\int f_t'(v_i)g(z_i-v_i)dv_i$$
$$=\mu_i\int f_t'(v_i)[g(z_i-u_i')+(v_i-u_i')g^{(1)}(z_i-u_i')$$

$$+(1/2)(v_i-u_i')^2 g^{(2)}(z_i-u_i')+\ldots]dv_i$$

$$=\mu_i[g(z_i-u_i')+(1/2)V_i' g^{(2)}(z_i-u_i')+\ldots],$$

where $V_i'=\int(v_i-u_i')^2 f_t'(v_i)dv_i$. If $g(z_i)$ is expressed by (3.5),

$$g^{(2)}(z_i-u_i')=(1/m_i^2)g(z_i-u_i')[(z_i-u_i')^2/m_i^2-1].$$

Then $\mu_i\int f_t'(v_i)g(z_i-v_i)dv_i$

$$=\mu_i g(z_i-u_i')[1+V_i'/(2m_i^2)\{(z_i-u_i')^2/m_i^2-1\}+\ldots]. \qquad (3.6)$$

An important observation of Turelli (1984) is that, under the reasonable assumption that $\mu_i \leqslant 10^{-4}$,

$$m_i^2 >> V_i', \qquad (3.7)$$

in which m_i^2 denotes the variance of effects associated with mutation and V_i' denotes the equilibrium allelic variance after selection. Then the second term and the terms in higher order in the bracket in (3.6) can be ignored without serious error, and (3.3) can be approximated by

$$f_{t+1}(z_i)=(1-\mu_i)f_t'(z_i)+\mu_i g(z_i-u_i') \qquad (3.8)$$

under the condition of (3.7). This is the "House-of-cards" approximation used by Turelli (1984) and originally introduced by Kingman (1978). In this approximation the effects of new mutants are assumed to be distributed around the population mean, and to be essentially independent of their premutation state. The density function of the equilibrium distribution of z_i in this approximation is given by

$$f_\infty(z_i)=\mu_i g(z_i-u_i)/[1-\xi w(z_i)], \qquad (3.9)$$

where ξ is a constant such that

$$\int f_\infty(z_i)dz_i=1, \qquad (3.10)$$

and $$u_i=\int z_i f_\infty(z_i)dz_i=\int z_i f_\infty'(z_i)dz_i. \qquad (3.11)$$

Thus, if $w(z_i)$ and $g(z_i-u_i)$ are known, $f_\infty(z_i)$ can be approximated by (3.9) providing $\mu_i \leqslant 10^{-4}$.

3.3. Allelic effect distribution at the limit to selection

In this section, (3.9) is used to find the equilibrium distribution of allelic effects z_i under stabilizing and truncation selection. First, consider $w(z_i)$, the selection function on z_i. Let $a_i=z_i-u_i$ be the excess of the allele z_i over the mean of alleles at the ith locus. The fitness of this allele, relative to the mean u_i, is usually given by

$$w(z_i)=\int f(x-a_i)w(x)dx/\int f(x)w(x)dx, \tag{3.12}$$

where $f(x)$ is the density function of phenotype and $w(x)$ is the selection function on phenotype. By expanding $f(x-a_i)$ in a Taylor series about x, we then have that, to order a_i^2,

$$w(z_i)=1+Ca_i+(1/2)Da_i^2, \tag{3.13}$$

where

$$C=-\int f^{(1)}(x)w(x)dx/\int f(x)w(x)dx$$

$$D=\int f^{(2)}(x)w(x)dx/\int f(x)w(x)dx.$$

If $f(x)$ is the normal density function with mean u and variance σ^2, then

$$C=\Delta u/\sigma^2$$

$$D=(\Delta\sigma^2+\Delta u^2)/\sigma^4,$$

where Δu and $\Delta\sigma^2$ are the changes in the mean and variance as a result of selection (Bulmer, 1980).

Since there are two kinds of selection, Δu and $\Delta\sigma^2$ are determined by two components. We have already found that in (2.7)

$$\Delta u = \iota\omega\sigma/(\sigma^2+\omega^2)^{1/2} - u\sigma^2/(\sigma^2+\omega^2). \tag{3.14}$$

From (2.3), we have that

$$\Delta\sigma^2(\textit{due to stabilizing}) = \sigma^2(1-\omega^2/(\sigma^2+\omega^2)) = -\sigma^4/(\sigma^2+\omega^2),$$

and it is well known that

$$\Delta\sigma^2(\textit{due to truncation}) = -\iota(\iota-Z)\sigma^2\omega^2/(\sigma^2+\omega^2),$$

where ι is the intensity of truncation selection and Z is the standard deviate of truncation point τ. So the total change in the variance due to selection is

$$\Delta\sigma^2 = -(\sigma^4 + \iota(\iota-Z)\sigma^2\omega^2)/(\sigma^2+\omega^2). \tag{3.15}$$

With (3.14) and (3.15), (3.13) becomes

$$w(z_i) = 1 + \frac{\iota\omega\sigma(\sigma^2+\omega^2)^{1/2} - u\sigma^2}{\sigma^2(\sigma^2+\omega^2)} a_i - \frac{\sigma^2+\iota(\iota-Z)\omega^2}{2\sigma^2(\sigma^2+\omega^2)} a_i^2. \tag{3.16}$$

In (3.16) Δu^2 is not included in the term of a_i^2. As shown later, this does not influence the results. When $a_i = z_i - u_i$ is small in magnitude, $w(z_i)$ can also be approximated by

$$w(z_i) \doteq \exp\{\frac{\iota\omega\sigma(\sigma^2+\omega^2)^{1/2} - u\sigma^2}{\sigma^2(\sigma^2+\omega^2)} a_i - \frac{\sigma^2+\iota(\iota-Z)\omega^2}{2\sigma^2(\sigma^2+\omega^2)} a_i^2\}$$

$$= \exp\{-(z_i-B)^2/(2A)\}\varepsilon, \tag{3.17}$$

where ε is a constant,

$$A = \frac{\sigma^2(\sigma^2+\omega^2)}{\sigma^2+\iota(\iota-Z)\omega^2}$$

and $$B = u_i + \frac{\iota\omega\sigma(\sigma^2+\omega^2)^{1/2} - u\sigma^2}{\sigma^2+\iota(\iota-Z)\omega^2}.$$

Now inserting (3.17) into (3.9) and letting $g(z_i-u_i)$ be defined by (3.5), we then have the following approximation for the density function of the distribution of allelic effects at the limit to

selection

$$f_{\infty}(z_i)=\frac{\mu_i \exp\{-(z_i-u_i)^2/(2m_i^2)\}}{(2\pi m_i^2)^{1/2}[1-\xi\exp\{-(z_i-B)^2/(2A)\}]}. \qquad (3.18)$$

It can be shown that in (3.18) $u_i=B$ *i.e.*,

$$u=\iota\omega(\sigma^2+\omega^2)^{1/2}/\sigma \qquad (3.19)$$

(see appendix for proof).

The result (3.19) has two implications: Firstly, since u_i in (3.18) could, in theory, take any value, but $u=\iota\omega(\sigma^2+\omega^2)^{1/2}/\sigma$, this shows that the mean genotype as well as the mean phenotype (since $u_x=u_y=u$ by assumption) is a fixed value at the limit to selection, but the mean effect of the alleles at a particular locus is not fixed. Their values at the selection limit would then largely depend on the initial conditions, historical influences and chance events at this particular locus. As a consequence, different lines or replicates in an experiment could be quite different in genetic constitution, even though they might show similar phenotypic expressions (see also Lande, 1975). Secondly, in contrast to the traditional argument that the maximum response to artificial selection is a function of the number of loci, *i.e.*, as the number of loci increases, the maximum response increases (*e.g.*, Robertson, 1960), this model predicts that the maximum response on the phenotype is independent of the number of genes responsible for the character. The increase in the number of loci is accompanied by a decrease in the effects of individual genes. Equation (3.19) for the maximum response at the limit to selection is identical to (2.10a).

Now let $a_i = z_i - u_i$. With $u = \iota\omega(\sigma^2+\omega^2)^{1/2}/\sigma$, (3.18) reduces to

$$f_\infty(a_i) = \frac{\mu_i \exp\{-a_i^2/(2m_i^2)\}}{(2\pi m_i^2)^{1/2}[1-\Xi\exp\{-a_i^2/(2A)\}]}, \tag{3.20}$$

which is the same as Turelli's equilibrium distribution of allelic effects under stabilizing selection alone. Here $A = \sigma^2(\sigma^2+\omega^2)/[\sigma^2+\iota(\iota-Z)\omega^2]$. By using Lerch's zeta function, Turelli (1984) has been able to show that

$$\begin{aligned} &\Xi \approx \exp\{-\mu_i^2 \pi A/m_i^2\} \\ &V_i = E(a_i^2) \approx 2\mu_i A \\ &r_2 = E(a_i^4)/[3\{E(a_i^2)\}^2] \approx m_i^2/(6\mu_i A) \end{aligned} \tag{3.21}$$

as $\mu_i \to 0$ for (3.20), where V_i is the equilibrium genetic variance due to locus i (haploid) and r_2 is the coefficient of kurtosis for this distribution. As he pointed out, the approximations rest on the condition that

$$\mu_i \ll m_i^2/A \ll 1, \tag{3.22}$$

which will be justified numerically in section 3.4.. In addition, it can easily be proved that this distribution is symmetric.

Considering all relevant loci, the total genetic variance can be approximated by

$$\sigma_y^2 = \sum_{i=1}^{n} 4\mu_i A, \tag{3.23a}$$

if a global linkage equilibrium is assumed. In particular, if the mutation rate is equal for all loci,

$$\sigma_y^2 = 4n\mu A = \frac{4n\mu\sigma^2(\sigma^2+\omega^2)}{\sigma^2+\iota(\iota-Z)\omega^2}. \tag{3.23b}$$

3.4. A check on the approximations

The results of (3.21) were obtained by Turelli (1984) from (3.20) as approximations, as $\mu_i \to 0$, *i.e.*, $\mu_i \ll m_i^2/A \ll 1$. This condition is internally consistent with $m_i^2 \gg V_i'$ (3.7) which leads (3.3) to (3.20) (Turelli, 1984). By a simulation of (3.3), Turelli provided a numerical test of the results of (3.21), which clarified the conditions for the house-of-cards approximation. In this section, I provide another numerical test of (3.21) directly from the moment calculation of (3.20) with truncation selection, which relies on Turelli's numerical calculation to support (3.20).

The numerical analysis was carried out as follows: First, given the values of μ, m^2, V_s ($V_s=\sigma^2+\omega^2$) and P, the parameter ξ of (3.20) was numerically found to satisfy $\int_{-\infty}^{\infty} f_\infty(a_i)da_i - 1 = 0$ by the Newton-Raphson method (see Gill, Murray and Wright, 1981). Then, with the estimate of ξ, the values of V, r_1 and r_2 were calculated by integrating the density function (3.20) for the first four moments, where r_1 is the coefficient of skewness.

In the computations, for convenience, all measurements except μ were scaled so that $\sigma=1$. The results of the computations are shown in Tables 3.1-4, which illustrate the effects on the analytically

predicted and numerically observed equilibrium genetic distribution of varying μ, m^2, V_s and P separately around $\mu=10^{-4}$, $m^2=0.05$, $V_s=10$ and $P=0.5$ with $u_i=0.1$ where $V_s=\sigma^2+\omega^2$. These values of parameters are chosen to be consistent with Turelli's analysis, so $V_s/\sigma^2=10$ is equivalent to $V_s/\sigma_e^2=20$ in Turelli (1984). The equilibrium genetic variance $[V]$ without truncation selection ($P=1$) is also presented in the tables for comparison. Since the distribution is symmetric, r_1 was found always to be zero and thus excluded from the tables.

The results of the variance $[V]$ for $P=1$ are very consistent with those of Turelli. As μ and V_s ($V_s=A$ in this case) decrease and m^2 increases, the approximate values of the variance became close to the observed values, and reasonable agreement between predicted and observed variances is achieved whenever $50\mu < m^2/V_s$ approximately (Tables 3.1-3). When $P=0.5$, the value of A ($A=\sigma^2V_s/[\sigma^2+(1-Z)\omega^2]$) is severely reduced. Although V_s ranges from 2 to 50 in Table 3.3, the value of A ranges only from 1.22 to 1.55. So the predicted variances displayed in Tables 3.1-3 are a little closer to the observed variances when $P=0.5$ than when $P=1$. Table 3.4 shows the effect of truncation selection on reducing the equilibrium genetic variance (see also Fig. 3.1 below). It is notable how severely the genetic variance is reduced by truncation selection.

Table 3.1

Effects of varying the mutation rate (μ) on the analytically predicted (Pre.) and numerically determined (Obs.) equilibrium genetic distribution for P=0.5, V_s=10 and m^2=0.05, given u_i=0.1.

μ		$\xi^{\dagger}$	u	V	$[V]$	r_2
10^{-3}	Pre.	0.9999067	7.57	2.97×10^{-3}	2.00×10^{-2}	5.61
	Obs.	0.9999164	7.57	2.75×10^{-3}	1.28×10^{-2}	6.70
10^{-4}	Pre.	0.999999067	7.57	2.97×10^{-4}	2.00×10^{-3}	5.61×10
	Obs.	0.999999077	7.57	2.97×10^{-4}	1.89×10^{-3}	5.76×10
10^{-5}	Pre.	0.99999999067	7.57	2.97×10^{-5}	2.00×10^{-4}	5.61×10^{2}
	Obs.	0.99999999068	7.57	2.99×10^{-5}	1.99×10^{-4}	5.67×10^{2}
10^{-6}	Pre.	0.99999999991	7.57	2.97×10^{-6}	2.00×10^{-5}	5.61×10^{3}
	Obs.	0.99999999991	7.57	2.99×10^{-6}	1.99×10^{-5}	5.67×10^{3}

† ξ is a parameter of (3.18).

$u=\iota\omega(\sigma^2+\omega^2)^{1/2}/\sigma$ is the mean genotype.

V is the variance of the distribution.

$[V]$ is the variance without truncation selection, *i.e.* when P=1.

$r_2=E(z_i-u_i)^4/\{3[E(z_i-u_i)^2]^2\}$ is the coefficient of kurtosis of the distribution.

Table 3.2

Effects of varying the variance of the effect for the mutants (m^2) for $\mu=10^{-4}$, $P=0.5$ and $V_s=10$, given $u_i=0.1$.

m^2		ξ	u	V	$[V]$	r_2
0.001	Pre.	0.99995333	7.57	2.97×10^{-4}	2.00×10^{-3}	1.12
	obs.	0.99997010	7.57	2.08×10^{-4}	5.83×10^{-4}	2.14
0.005	Pre.	0.99999067	7.57	2.97×10^{-4}	2.00×10^{-3}	5.61
	obs.	0.99999164	7.57	2.73×10^{-4}	1.28×10^{-3}	6.65
0.01	Pre.	0.99999533	7.57	2.97×10^{-4}	2.00×10^{-3}	1.12×10
	obs.	0.99999559	7.57	2.85×10^{-4}	1.55×10^{-3}	1.23×10
0.05	Pre.	0.99999907	7.57	2.97×10^{-4}	2.00×10^{-3}	5.61×10
	obs.	0.99999908	7.57	2.97×10^{-4}	1.89×10^{-3}	5.76×10
0.1	Pre.	0.999999533	7.57	2.97×10^{-4}	2.00×10^{-3}	1.12×10^{2}
	obs.	0.999999536	7.57	3.01×10^{-4}	1.94×10^{-3}	1.15×10^{2}
0.5	Pre.	0.9999999067	7.57	2.97×10^{-4}	2.00×10^{-3}	5.61×10^{2}
	obs.	0.9999999068	7.57	3.24×10^{-4}	2.01×10^{-3}	6.07×10^{2}

Table 3.3

Effects of varying the intensity of stabilizing selection (V_s) for $\mu=10^{-4}$, $P=0.5$ and $m^2=0.05$, given $u_i=0.1$.

V_s		$\bar{\xi}$	u	V	$[V]$	r_2
2	Pre.	0.999999232	1.13	2.44×10^{-4}	4.00×10^{-4}	6.82x10
	Obs.	0.999999240	1.13	2.45×10^{-4}	3.98×10^{-4}	6.99x10
5	Pre.	0.999999114	3.57	2.82×10^{-4}	1.00×10^{-3}	5.91x10
	Obs.	0.999999124	3.57	2.82×10^{-4}	9.72×10^{-4}	6.07x10
10	Pre.	0.99999907	7.57	2.97×10^{-4}	2.00×10^{-3}	5.61x10
	Obs.	0.99999908	7.57	2.97×10^{-4}	1.89×10^{-3}	5.76x10
15	Pre.	0.99999905	11.56	3.03×10^{-4}	3.00×10^{-3}	5.51x10
	Obs.	0.99999906	11.56	3.02×10^{-4}	2.75×10^{-3}	5.66x10
20	Pre.	0.99999904	15.56	3.05×10^{-4}	4.00×10^{-3}	5.46x10
	Obs.	0.99999905	15.56	3.04×10^{-4}	3.57×10^{-3}	5.61x10
50	Pre.	0.99999903	39.50	3.11×10^{-4}	1.00×10^{-2}	5.37x10
	Obs.	0.99999904	39.50	3.10×10^{-4}	7.73×10^{-3}	5.52x10

Table 3.4

Effects of varying the proportion of truncation selection (P) for $\mu=10^{-4}$, $V_s=10$ and $m^2=0.05$, given $u_i=0.1$.

P		ξ	u	V	r_2
1.0	Pre.	0.9999937	0.00	2.00×10^{-3}	8.33
	Obs.	0.9999942	0.00	1.89×10^{-3}	9.39
0.9	Pre.	0.99999825	1.85	5.57×10^{-4}	2.99×10
	Obs.	0.99999829	1.85	5.50×10^{-4}	3.11×10
0.7	Pre.	0.99999887	4.71	3.59×10^{-4}	4.64×10
	Obs.	0.99999889	4.71	3.58×10^{-4}	4.78×10
0.5	Pre.	0.99999907	7.57	2.97×10^{-4}	5.61×10
	Obs.	0.99999908	7.57	2.97×10^{-4}	5.76×10
0.3	Pre.	0.999999176	11.00	2.62×10^{-4}	6.35×10
	Obs.	0.999999184	11.00	2.63×10^{-4}	6.52×10
0.1	Pre.	0.999999258	16.65	2.36×10^{-4}	7.06×10
	Obs.	0.999999265	16.65	2.37×10^{-4}	7.24×10

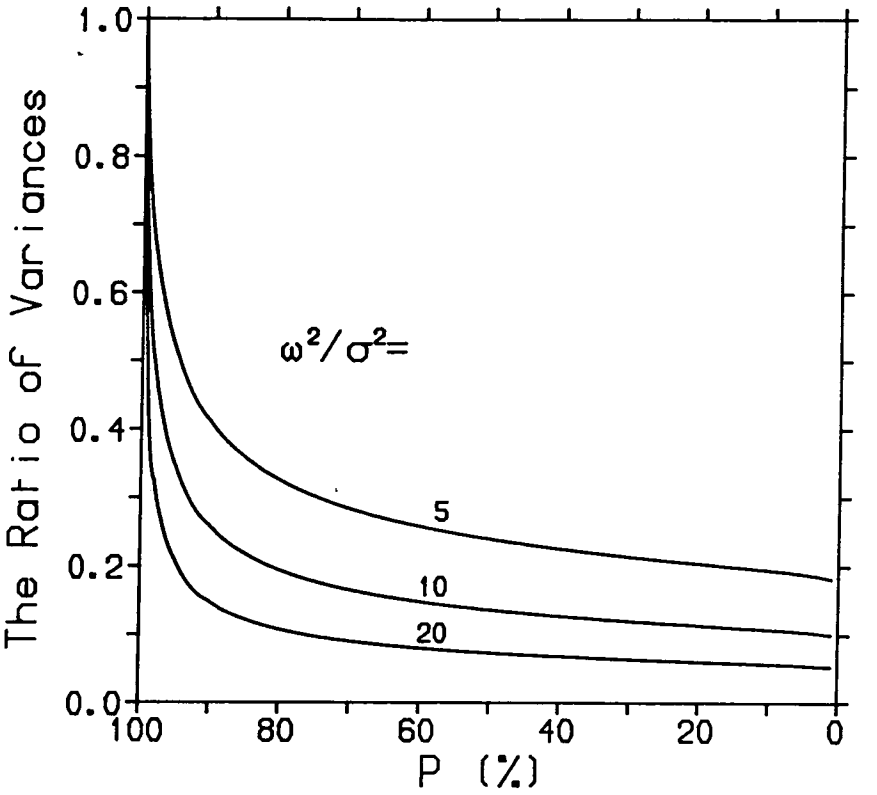

Fig. 3.1: The ratio of genetic variances maintained by the balance with and without truncation selection is plotted against the proportion of truncation selection ($P\%$) for different values of ω^2/σ^2. The ratio is equal to $[1+t(t-Z)\omega^2/\sigma^2]^{-1}$.

3.5. Discussion

The maintenance of genetic variability has been the central argument of many researches. In an influential paper which combined mathematical analysis with a review of relevant data, Lande (1975) proposed that high levels of variation could be maintained by mutation in the face of stabilizing selection. This proposal was reviewed by Turelli (1984) in the light of mathematical and empirical evidence. Although there are some differences in the assumptions and predictions between Lande's and Turelli's approximations, the observations made by Turelli basically agreed with Lande's argument.

If the mutation-selection balance can account for high levels of genetic variability in the face of stabilizing selection, this balance may or may not be sufficient to explain the maintenance of genetic variability when additional truncation selection is taken into account in the model. Fig. 3.1 shows the ratio of genetic variances maintained by the balance with and without truncation selection for different values of ω^2/σ^2 and P. It can be seen that truncation selection is a crucial factor in quantifying the equilibrium genetic variance. Even a small amount of selection can severely reduce the variance. But when selection is strong any further increase in the strength of selection has little further influence on the variance. To determine the heritability likely maintained in a population at the selection limit, we need to estimate the values of parameters $n\mu$ and ω^2/σ^2. Relevant data for estimating $n\mu$ and ω^2/σ^2 has been reviewed by Turelli (1984) who

considered that $n\mu \approx 0.01$ and $\omega^2/\sigma^2 \approx 5\text{-}10$ might be the typical estimates for many quantitative characters. With those values the house-of-cards approximation predicts heritabilities ($h^2=4n\mu(\sigma^2+\omega^2)/[\sigma^2+\iota(\iota-Z)\omega^2]$) ranging from 0.240 to 0.440 without truncation selection, but 0.098-0.113 for $P=0.9$ and 0.057-0.060 for $P=0.5$. This seems to suggest that in the presence of opposing truncation selection the heritability can only be maintained at a low level with $n\mu=0.01$. In this case the change in the intensity of stabilizing selection does not make a significant difference to the variance. However, if $n\mu$ is 0.02 rather then 0.01, the heritability at the selection limit would be about 0.303-0.088 for $P=0.095\text{-}0.01$ and $\omega^2/\sigma^2=10$. Clearly, the argument relies on the estimation of the relevant parameters, particularly the total mutation rate of the loci controlling the character concerned.

3.6. Summary

Both Lande (1975) and Turelli (1984) suggested that high levels of genetic variation could be maintained by mutation in the face of stabilizing selection in their analyses on a model introduced by Kimura (1965). This model is used to examine the maintenance of genetic variability at the selection limit with Turelli's "house-of-cards" approximation. When this approximation is extended to include truncation selection, it is found that in this case truncation selection can substantially reduce the equilibrium genetic variance below that when only stabilizing selection is acting, and the proportional reduction in the variance is greatest when the truncation selection is very weak. When truncation selection is

strong, any further increase in the strength of selection has little further influence on the variance. It appears that this mutation-selection balance is insufficient to account for the high levels of genetic variation observed in many long-term selection experiments.

CHAPTER 4

GENOTYPIC DISTRIBUTION AT THE LIMITS TO SELECTION

4.1. Introduction

The results of chapter 2 were obtained under the assumption that the distribution of phenotype maintains Gaussian in each generation before selection. Strictly speaking, this assumption can hardly hold in the face of continuous selection, particularly truncation. So when we discuss the long-term consequences of the conflict between stabilizing and truncation selection, the approximate validity of the assumption of Gaussian distributions of genotypes and phenotypes needs to be investigated.

In this chapter, the robustness of Gaussian approximations under the long-term continuous natural and artificial selection is examined, and particular attention is given to the genotypic distribution at the limits to selection. The role of mutation on long-term response and selection limits is also discussed.

4.2. The theory

4.2.1. *Specification of problem*

Consider a quantitative character with phenotypic value (X) codetermined by genotypic value (Y) and environmental effect (E) according to

$$X=Y+E. \qquad (4.1)$$

It is assumed as in the early chapters that stabilizing selection acts on the phenotype, so that the fitness of an individual is merely a function of its phenotypic deviation from an intermediate optimum, and truncation selection is practised so that in each generation a fraction P of individuals with the highest (or lowest in downward selection) measured values of X is selected. However, because genotypic values (Y) are transmitted from generation to generation but individual values of Y cannot be measured, the nature of the distribution of Y after selection can only be inferred from that of X, so the procedure for analyses of life cycle is as follows: (i) given a distribution of Y before selection, we first find the distribution of X making some assumptions about the distribution of E; (ii) we then examine the change of distribution of X due to stabilizing selection followed by truncation selection; (iii) we next determine the distribution of Y conditional on X after selection; and (iv) finally we examine the relation between the distributions of Y after selection and in the next generation before selection. The analysis will be based on an expansion of distribution in terms of the corresponding normal distribution —— the Gram-Charlier expansion —— in the univariate and bivariate cases.

Let $f(X,Y)$ be the probability density function (p.d.f) of X,Y for which all the product moments exist, and let

$$\varphi(X,Y)=\frac{1}{2\pi\sigma_x\sigma_y(1-\varrho^2)}\exp\{-\frac{1}{2(1-\varrho^2)}[\frac{(X-u_x)^2}{\sigma_x^2}-\frac{2(X-u_x)(Y-u_y)}{\sigma_x\sigma_y\varrho}+\frac{(Y-u_y)^2}{\sigma_y^2}]\} \tag{4.2}$$

be the corresponding bivariate normal p.d.f., where u_x, u_y, σ_x^2 and

σ_y^2 are the means and variances of X and Y and ϱ is the correlation coefficient between X and Y.

In this chapter I will frequently use another set of descriptive constants of a distribution, the cumulants. Because of their special properties, such as invariance of all but the first cumulants to change of origin, they are very useful for specifying a distribution. Let k_{ij} be the cumulants of order (i,j) of X,Y. We have

$$k_{10}=u_x,\ k_{01}=u_y;$$
$$k_{20}=\sigma_x^2,\ k_{11}=\sigma_x\sigma_y\varrho,\ k_{02}=\sigma_y^2$$

(for the relation between moments and cumulants for $i+j>2$ see Kendall and Stuart, 1969, p. 81-84). Then by the Gram-Charlier expansion, $f(X,Y)$ can be expanded as a series in terms of derivatives of $\varphi(X,Y)$,

$$f(X,Y) = \varphi(X,Y) + \sum_{i+j\geq 3} (-1)^{i+j} k_{ij} \frac{D_X^i}{i!} \frac{D_Y^j}{j!} \varphi(X,Y), \qquad (4.3)$$

where $D_X=\partial/\partial X$ and $D_Y=\partial/\partial Y$ (see Mardia, 1970, p. 12-13). Similarly the marginal p.d.f of X can be expanded in terms of $\varphi(X,0)$,

$$f(X) = \varphi(X,0) + \sum_{i\geq 3} (-1)^i k_{i0} \frac{D_X^i}{i!} \varphi(X,0) \qquad (4.4)$$

(see Johnson and Kotz, 1970, p. 16-17). The above infinite series (4.3) and (4.4) are called Gram-Charlier series, and usually only the first few terms can be taken into account. In this chapter we restrict our attention to the case where $i+j \leq 4$ (for the problems of the use of this approach see Johnson and Kotz, 1970, p. 18-19 and Mardia, 1970, p. 23).

If we further assume that the environmental effect is an independently normally distributed variate with mean zero and

variance σ_e^2, the cumulants k_{ij} of the joint distribution of X,Y are easily seen to be

$$k_{ij}=k_{0,i+j}, \tag{4.5}$$

except that

$$k_{20}=\sigma_y^2+\sigma_e^2=\sigma_x^2.$$

If the distribution of the environmental effect is neither independent, nor normal, and the cumulants of the joint distribution of Y,E are defined by K_{jl}, the cumulants k_{ij} of the joint distribution of X,Y can be calculated from K_{jl} (see Eq.(2.4) of Finney, 1961). But this situation will not be considered here.

Furthermore, it is convenient for analysis to standardize the variates, by writing

$$x=(X-u_x)/\sigma_x,\quad y=(Y-u_y)/\sigma_y;$$

$$D_x=D_X/\sigma_x,\quad D_y=D_Y/\sigma_y; \tag{4.6}$$

and $\gamma_{ij}=k_{ij}/(\sigma_x^i\sigma_y^j)$,

so that $\gamma_{10}=\gamma_{01}=0$; and $\gamma_{20}=\gamma_{02}=1$, $\gamma_{11}=\varrho$. Then, (4.3) and (4.4) can be written as

$$f(x,y) = [\ 1 + \sum_{3\leq i+j\leq 4} (-1)^{i+j}\ \gamma_{ij}\ \frac{D_x^{\,i}}{i!}\ \frac{D_y^{\,j}}{j!}\ ]\ \varphi(x,y), \tag{4.7}$$

and

$$f(x) = [\ 1 + \frac{1}{3!}\gamma_{30}H_3(x) + \frac{1}{4!}\gamma_{40}H_4(x)\ ]\ \varphi(x), \tag{4.8}$$

where $\varphi(x,y)$ and $\varphi(x)$ are standardized normal density functions, and $H_r(x)$ is the Hermite polynomial of the rth order which satisfies

$$D_x^{\,r}\varphi(x)=(-1)^r H_r(x)\varphi(x), \tag{4.9}$$

so $H_1(x)=x$

$$H_2(x)=x^2-1$$

$$H_3(x)=x^3-3x$$

$$H_4(x)=x^4-6x^2+3.$$

4.2.2. *Selection*

4.2.2.1. *Selection from a normal distribution*

A particularly simple version of the problem, and one in terms of which more general results will eventually be expressed, is that for which Y (and therefore X) is normally distributed. This means that

$$k_{ij}=0 \qquad \text{for } i,j>2. \tag{4.10}$$

If the function describing stabilizing selection is taken to be

$$w(X)=\exp\{-X^2/(2\omega^2)\}, \tag{4.11}$$

as in the early chapters, the p.d.f of X after stabilizing selection is

$$f'(X) = \varphi(X)w(X)/\int\varphi(X)w(X)dX$$

$$= \frac{1}{\sqrt{(2\pi c\sigma_x^2)}}\exp\{-\frac{(X-cu_x)^2}{2c\sigma_x^2}\}, \tag{4.12}$$

where $c=\omega^2(\omega^2+\sigma_x^2)^{-1}$.

Now consider truncation selection. Let z be the truncation point in standard deviations from the mean corresponding to the proportion selected P. Then the rth moment of the standardized truncated normal distribution is

$$m_r = P^{-1}\int_z^{\infty} x^r\varphi(x)dx, \tag{4.13}$$

where $P=\int_{Z}^{\infty}\varphi(x)dx$. Equation (4.13) can be calculated from

$$m_r = \left[Z^{r-1} + \sum_{j=1}^{r/2-1} (r-1)(r-3)\ldots(r-2j+1)Z^{r-2j-1} \right] \iota + \frac{r!}{2^{r/2}(r/2)!}$$

for r even,

$$m_r = \left[Z^{r-1} + \sum_{j=1}^{(r-1)/2} (r-1)(r-3)\ldots(r-2j+1)Z^{r-2j-1} \right] \iota$$

for r odd. (4.14)

(Elandt, 1961), where $\iota=\varphi(Z)/P$, is the intensity of truncation selection. Hence, with cu_x and $c\sigma_x^2$ being the mean and variance of the underlying distribution before truncation, the mean, variance, third and fourth cumulants of X after selection are

$$\begin{aligned} u_x^* &= cu_x + \iota c^{1/2}\sigma_x, \\ \sigma_x^{*2} &= [1-\iota(\iota-Z)]c\sigma_x^2, \\ k_{3x}^* &= [(\iota-Z)(2\iota-Z)-1]\iota c^{3/2}\sigma_x^3, \\ k_{4x}^* &= [-6\iota(\iota-Z)^2+(3-Z^2)(\iota-Z)+\iota]\iota c^2\sigma_x^4, \end{aligned} \qquad (4.15)$$

(see also Bulmer, 1980, p. 153).

Transition from here to the cumulants of Y is simple. Since the joint distribution of X and Y is bivariate normal before selection, then the regression of Y on X is linear

$$E(Y|X)=u_y+h^2(X-u_x) \qquad (4.16)$$

with $Var(Y|X)=(1-h^2)\sigma_y^2$,

where $h^2=\sigma_y^2/\sigma_x^2$ is the heritability. Since truncation on X does not affect the regression of Y on X (Rao *et al*, 1968), the cumulants of Y after selection are therefore

$$u_y^* = u_x[1-h^2(1-c)]+h^2\iota c^{1/2}\sigma_x,$$

$$\sigma_y^{*2} = \sigma_y^2 [1 - h^2(1-c) - h^2 c(c-Z)], \tag{4.17}$$

$$k_{ry}^* = k_{rx}^* h^{2r} \qquad \text{for } r>2.$$

4.2.2.2. *General approach*

When $f(X,Y)$ is completely general in form, the method of computing the distribution of Y must be changed. Finney (1956,1961) attacked this problem by considering the integration of the conditional moment generating function of y on x over the frequency distribution of x, and obtained what appeared to be general results for the moment generating function of y after selection, but his concise formula (Eq.(5.5) of Finney, 1961) appears to be of little direct use for calculation, though the explicit expressions for the first four moments of y after selection were given in the case of truncation selection.

Karl Pearson (1925) investigated the distribution of (4.3) for terms up to i+j=4 and called it a fifteen constant bivariate distribution; the fifteen constants being the constant of total frequency, the first four moments of each margin and k_{11}, k_{12}, k_{21}, k_{22}, k_{31}, k_{13}. He obtained the first two conditional moment curves for this fifteen constant surface which are

$$E(y|x) = \varrho x + B_x/A_x \tag{4.18}$$

$$E(y^2|x) = (1-\varrho^2) + \varrho^2 x^2 - C_x/A_x + 2\varrho x B_x/A_x, \tag{4.19}$$

where

$$A_x = 1 + (1/6)\gamma_{30}H_3(x) + (1/24)\gamma_{40}H_4(x)$$

$$= 1 + a_3 H_3(x) + a_4 H_4(x),$$

$$B_x = (1/2)(\gamma_{21} - \varrho\gamma_{30})H_2(x) + (1/6)(\gamma_{31} - \varrho\gamma_{40})H_3(x)$$

$$= b_2 H_2(x) + b_3 H_3(x),$$

$$C_x = \{\varrho(\gamma_{21} - \varrho\gamma_{30}) - (\gamma_{12} - \varrho\gamma_{21})\} H_1(x) + (1/2)\{2\varrho(\gamma_{31} - \varrho\gamma_{40}) - \gamma_{22} + \varrho^2\gamma_{40}\} H_2(x)$$

$$= c_1 H_1(x) + c_2 H_2(x).$$

Later, Pretorius (1930) further investigated this fifteen constant surface, and got the third and fourth conditional moment curves

$$E(y^3|x) = 3\varrho(1-\varrho^2)x + \varrho^3 x^3 + D_x/A_x - 3\varrho x C_x/A_x + 3(1-\varrho^2+\varrho^2x^2)B_x/A_x, \quad (4.20)$$

$$E(y^4|x) = [3(1-\varrho^2)^2 + 6\varrho^2(1-\varrho^2)x^2 + \varrho^4 x^4] + e_0/A_x + 4\varrho x D_x/A_x$$

$$-6[\varrho^2(x^2-1)+1]C_x/A_x + 4[\varrho^3(x^3-3x) + 3\varrho x]B_x/A_x, \quad (4.21)$$

where

$$D_x = \{(\gamma_{03} - \varrho^3\gamma_{30} - 3\varrho(\gamma_{12} - \varrho\gamma_{21})\} + \{\gamma_{13} - 3\varrho\gamma_{22} + 3\varrho^2\gamma_{31} - \varrho^3\gamma_{40}\} H_1(x)$$

$$= d_0 + d_1 H_1(x),$$

$$e_0 = \gamma_{04}(1-4\varrho^2) - 3\varrho^4\gamma_{40} + 6\varrho^2\gamma_{22} - 4\varrho(\gamma_{13} - \varrho\gamma_{04}) - 4\varrho^3(\gamma_{31} - \varrho\gamma_{40}).$$

It is of interest to see the conditions for linearity of regression by letting $B_x = 0$,

i.e., $\gamma_{21} = \varrho\gamma_{30}$ and $\gamma_{31} = \varrho\gamma_{40}$; (4.22)

which are equivalent to

$$k_{3y}/\sigma_y^2 = k_{3e}/\sigma_e^2 \text{ and } k_{4y}/\sigma_y^2 = k_{4e}/\sigma_e^2. \quad (4.23)$$

These are the conditions stated by Lindley (1947), namely that the cumulant generating function of Y is a multiple of that of E.

The moments of the distribution of y after selection can then be obtained by taking expected values of x after selection in (4.18)-(4.21). Note that when $f(x,y)$ is bivariate normal, (4.18) and (4.19) reduce to (4.16) except that x and y here are standardized and $\varrho = h$. The fitness function with a standardized variate becomes

$$w(x) = \exp[-(x\sigma_x + u_x)^2/(2\omega^2)] \quad (4.24)$$

from (4.11). From (4.8) and (4.24), the p.d.f of x, after

stabilizing selection, is then found to be

$$f'(x)=f(x)w(x)/\int f(x)w(x)dx$$
$$=[1+(1/6)\gamma'_{30}H_3(x')+(1/24)\gamma'_{40}H_4(x')]\varphi(x')/s$$
$$=A_x\cdot\varphi(x')/s, \qquad (4.25)$$

where $x'=(x-v)/s$, $v=-u_x\sigma_x/(\sigma_x^2+\omega^2)$, $s=\{\omega^2/(\sigma_x^2+\omega^2)\}^{1/2}$;

and $\gamma'_{30}=\gamma_{30}/s^3$, $\gamma'_{40}=\gamma_{40}/s^4$.

Before proceeding to calculation of the effect of truncation selection, the truncation point needs to be determined since the shape of the distribution is changed. Suppose that T is the truncation point corresponding to a proportion P of the population, i.e.,

$$P=\int_T^\infty f'(x)dx', \qquad (4.26)$$

and define Z as the unit normal deviate corresponding to the same proportion P,

$$P=\int_Z^\infty \varphi(x)dx. \qquad (4.27)$$

Then by using Cornish and Fisher's (1937) expansion, the value of T can be written as an infinite series in terms of Z which is approximately

$$T\approx Z+(1/6)\gamma'_{30}(Z^2-1)+(1/24)\gamma'_{40}(Z^3-3Z)-(1/36)\gamma'^2_{30}(2Z^2-5Z). \qquad (4.28)$$

Now let

$$m_r=P_T^{-1}\int_T^\infty x'^r\varphi(x')dx', \qquad (4.29)$$

where

$$P_T = \int_T^\infty \varphi(x')dx', \tag{4.30}$$

which can be calculated from (4.14). Thus, the moments of the distribution of x after selection are

$$u_x^{*r} = P^{-1}\int_T^\infty x'^r f'(x)dx'$$

$$= [m_r + (1/6)\gamma'_{30}(m_{r+3} - 3m_{r+1}) + (1/24)\gamma'_{40}(m_{r+4} - 6m_{r+2} + 3m_r)]P_T/P. \tag{4.31}$$

Unlike the case of the Gaussian approximation, the transition from here to the moments of y is rather complicated. There is a slight problem in our selection scheme in using (4.18)-(4.21), in that A_x has been changed to $A_{x'}$ after stabilizing selection. If the distribution we are dealing with differs not much from the normal, the denominator in (4.18)-(4.21) (*i.e.*, A_x) may be put to unity. This simplification greatly facilitates the calculation of u_y^{*r}. It has been proved by numerical integration that this simplification introduces little error to the approximations, just slightly underestimating the variance and overestimating the mean, skewness and kurtosis. The error introduced is only about 0.01 for the distribution with the coefficients of skewness and kurtosis up to 1.

To obtain u_y^{*r}, it is necessary to have x in (4.18)-(4.21) transformed into x'. Since

$$x = sx' + v,$$

we have

$$B_x = b_2(x^2 - 1) + b_3(x^3 - 3x)$$

$$= \{b_2(v^2 - 1) + b_3(v^3 - 3v)\} + \{2b_2sv + 3b_3s(v^2 - 1)\}x'$$

$$+ \{b_2s^2 + 3b_3s^2v\}x'^2 + \{b_3s^3\}x'^3$$

$$= B_0 + B_1 x' + B_2 x'^2 + B_3 x'^3,$$

$$C_x = c_1 x + c_2 (x^2 - 1)$$

$$= \{c_1 v + c_2 (v^2 - 1)\} + \{c_1 s + 2 c_2 s v\} x' + \{c_2 s^2\} x'^2$$

$$= C_0 + C_1 x' + C_2 x'^2,$$

$$D_x = d_0 + d_1 x$$

$$= \{d_0 + d_1 v\} + \{d_1 s\} x'$$

$$= D_0 + D_1 x',$$

and then, from (4.18) and (4.19),

$$u_y^* = E\{E(y|x)\}$$

$$= \varrho (v + s u_x^*) + B_0 + B_1 u_x^* + B_2 u_x^{*2} + B_3 u_x^{*3}, \tag{4.32}$$

and

$$u_y^{*2} = E\{E(y^2|x)\}$$

$$= 1 - \varrho^2 + \varrho^2 (v^2 + 2 v s u_x^* + s^2 u_x^{*2}) - C_0 - C_1 u_x^* - C_2 u_x^{*2}$$

$$+ 2\varrho [v B_0 + (v B_1 + s B_0) u_x^* + (v B_2 + s B_1) u_x^{*2}$$

$$+ (v B_3 + s B_2) u_x^{*3} + s B_3 u_x^{*4}]. \tag{4.33}$$

Similarly, from (4.20) and (4.21),

$$u_y^{*3} = E\{E(y^3|x)\}$$

$$= 3\varrho (1 - \varrho^2)(v + s u_x^*) + \varrho^3 (v^3 + 3 v^2 s u_x^* + 3 v s^2 u_x^{*2} + s^3 u_x^{*3})$$

$$+ D_0 + D_1 u_x^* - 3\varrho [v C_0 + (v C_1 + s C_0) u_x^* + (v C_2 + s C_1) u_x^{*2} + s C_2 u_x^{*3}]$$

$$+ 3 [V_0 B_0 + (V_0 B_1 + V_1 B_0) u_x^* + (V_0 B_2 + V_1 B_1 + V_2 B_0) u_x^{*2}$$

$$+ (V_0 B_3 + V_1 B_2 + V_2 B_1) u_x^{*3} + (V_1 B_3 + V_2 B_2) u_x^{*4} + V_2 B_3 u_x^{*5}], \tag{4.34}$$

and

$$u_y^{*4} = E\{E(y^4|x)\}$$

$$= 3(1 - \varrho^2)^2 + 6\varrho^2 (1 - \varrho^2)(v^2 + 2 v s u_x^* + s^2 u_x^{*2})$$

$$+ \varrho^4 (v^4 + 4 v^3 s u_x^* + 6 v^2 s^2 u_x^{*2} + 4 v s^3 u_x^{*3} + s^4 u_x^{*4}) + e_0$$

$$+ 4\varrho [v D_0 + (v D_1 + s D_0) u_x^* + s D_1 u_x^{*2}] - 6 [V_0 C_0 + (V_0 C_1 + V_1 C_0) u_x^*$$

$$+ (V_0 C_2 + V_1 C_1 + V_2 C_0) u_x^{*2} + (V_1 C_2 + V_2 C_1) u_x^{*3} + V_2 C_2 u_x^{*4}]$$

$$+4[W_0B_0+(W_0B_1+W_1B_0)u_x^{*}+(W_0B_2+W_1B_1+W_2B_0)u_x^{*2}$$
$$+(W_0B_3+W_1B_2+W_2B_1+W_3B_0)u_x^{*3}+(W_1B_3+W_2B_2+W_3B_1)u_x^{*4}$$
$$+(W_2B_3+W_3B_2)u_x^{*5}+W_3B_3u_x^{*6}], \qquad (4.35)$$

where $V_0=\varrho^2v^2+1-\varrho^2$

$V_1=2\varrho^2vs$

$V_2=\varrho^2s^2$

$W_0=\varrho^3v^3+3\varrho v(1-\varrho^2)$

$W_1=3\varrho^3v^2s+3\varrho s(1-\varrho^2)$

$W_2=3\varrho^3vs^2$

$W_3=\varrho^3s^3$.

The cumulants of y and also of Y can be derived from (4.32)-(4.35).

4.2.3. *Reproduction*

4.2.3.1. *Infinitesimal model*

Consider a character which is controlled by a very large number of loci with infinitesimal effects. Bulmer (1980) showed that if the epistatic effects between the loci are ignored, the regression of the genotypic value of an individual (Y_c), measured before selection, on the genotypic values of his parents (Y_f, Y_m) is

$$E(Y_c|Y_f,Y_m)=(1/2)Y_f+(1/2)Y_m \qquad (4.36)$$

with the residual variance about the regression

$$Var(Y_c|Y_f,Y_m)=(1/2)\sigma_g^2, \qquad (4.37)$$

where σ_g^2 is the genic variance of the character which is the variance calculated from the gene frequencies at Hardy-Weinberg and linkage

equilibrium. In particular if selection acts equally on the two sexes and mating is random, so that Y_f and Y_m are independently and identically distributed, the cumulants of Y then satisfy the relationship

$$k_{ry}(t+1)=(1/2)^{r-1}k_{ry}^{*}(t),\quad r=1,3,4,\ldots \tag{4.38}$$

and when $r=2$,

$$k_{2y}(t+1)=(1/2)k_{2y}^{*}(t)+(1/2)\sigma_g^2, \tag{4.39}$$

where $k_{ry}^{*}(t)$ are the rth cumulants of Y in generation t after selection and $k_{ry}(t+1)$ are those in the next generation before selection (see Bulmer, 1980, p. 148).

It is seen that any change in the mean due to selection will be entirely transmitted to the next generation, but only one-half of the change in variance will remain in the next generation, and for the third and fourth cumulants, one-quarter and one-eighth respectively. Bulmer explained that selection acts in two ways, by changing gene frequencies and by inducing departures from Hardy-Weinberg and linkage equilibrium. The change due to gene frequency will be permanent, but that due to the build-up of linkage disequilibrium is only temporary and will gradually disappear when selection is relaxed. Since linkage disequilibrium has no effect on the mean in the absence of epistatic interactions, any changes in the mean must be due to change in gene frequencies and will be permanent. On the other hand, since the model presupposes an effectively infinite number of loci with infinitesimal effects, a finite change in the mean can be brought about by an infinitesimal change in each of the gene frequencies which will have negligible effect on the variance and the higher moments in the absence of linkage disequilibrium.

Thus any change in the variance and the higher moments is due to linkage disequilibrium and will gradually disappear when selection is relaxed.

4.2.3.2. *n-locus model*

When we discuss the long-term response to selection, the cumulative effects of gene frequency changes on the variance and the higher moments are not negligible because the number of loci is unlikely to be very large in practice. It seems that the number of loci for most quantitative characters is about 20-400 (Falconer, 1981). With this range of number of loci, the genetic variance could be changed drastically during the course of long-term directional selection due to the change of gene frequencies.

The change of gene frequencies depends on the number, effects and frequencies of genes involved, information which on the whole is not available, particularly for the case of quantitative characters. To make the situation easy to handle, let us consider a simple model in which we suppose that a character is determined by n loci and each locus contains two additive alleles with the effect of gene substitution a (in units of phenotypic standard deviation in the base population) in single dose and $2a$ in double dose. Further, we assume equal effects and frequencies of the genes over all the loci, an assumption which is highly unrealistic. Then, the cumulants of Y in Hardy-Weinberg and linkage equilibrium are easily seen to be (from the binomial distribution with $2n$ members)

$$u_y = 2nap$$

$$\sigma_g^2 = 2na^2pq \tag{4.40}$$

$$k_{3g} = 2na^3pq(p-q)$$

$$k_{4g} = 2na^4pq(1-6pq)$$

and the coefficients of skewness and kurtosis are

$$\gamma_{3g} = \frac{p-q}{\sqrt{(2npq)}} \tag{4.41}$$

$$\gamma_{4g} = \frac{1-6pq}{2npq} ,$$

so that, as $n \to \infty$, γ_{3g} and $\gamma_{4g} \to 0$, where p is the frequency of the allele favoured by selection and $q=1-p$.

Since the change in the mean is the result of gene frequency shift (ignoring epistatic interactions), the change in p due to selection is then

$$\Delta p = \frac{u_y^* - u_y}{2na} . \tag{4.42}$$

Therefore, $\Delta\sigma_g^2$, the change in variance due to gene frequency shift, can be calculated from (4.42) and (4.40). Let $\Delta\sigma_d^2$ represent the contribution to the change in variance due to linkage disequilibrium and $\Delta\sigma_y^2$ represent the change of the genotypic variance, so that

$$\Delta\sigma_y^2 = \Delta\sigma_g^2 + \Delta\sigma_d^2 . \tag{4.43}$$

From (4.39) and (4.43), we thus have

$$\sigma_y^2(t+1) = \sigma_g^2(t) + \Delta\sigma_g^2 + (1/2)\sigma_d^2(t) + (1/2)\Delta\sigma_d^2 . \tag{4.44}$$

The same argument can apply to the higher cumulants. Then we also have

$$k_{3y}(t+1) = k_{3g}(t) + \Delta k_{3g} + (1/4)k_{3d}(t) + (1/4)\Delta k_{3d}$$

and (4.45)

$$k_{4y}(t+1)=k_{4g}(t)+\Delta k_{4g}+(1/8)k_{4d}(t)+(1/8)\Delta k_{4d}.$$

Finally, if we ignore the departure from normality as a first approximation, we can now find an recurrence relationship for the mean and variance under continued stabilizing and truncation selection:

$$u_y(t+1)=u_y(t)[1-h^2(t)(1-c)]+h^2(t)\iota c^{1/2}\sigma_x \tag{4.46}$$

$$\sigma_y^2(t+1)=(1/2)\sigma_y^2(t)[1-h^2(t)(1-c)-h^2(t)c\iota(\iota-Z)]+(1/2)\sigma_g^2(t) \tag{4.47}$$

from (4.17), (4.38) and (4.44), where $\sigma_g^2(t)=2na^2p(t)\{1-p(t)\}$ and $p(t)$ is the mean gene frequency at generation t. So at the limit, the population mean and variance can be found to be

$$u_y(\infty)=(\iota/\sigma_x)\{\omega^2(\sigma_x^2+\omega^2)\}^{1/2}, \tag{4.48}$$

$$\sigma_y^2(\infty)=\frac{\sigma_x^2[\{1+4(1-c+c\iota(\iota-Z)\sigma_g^2/\sigma_x^2\}^{1/2}-1]}{1-c+c\iota(\iota-Z)}, \tag{4.49}$$

in units of phenotypic standard deviation in the base population, where σ_g^2 and σ_x^2 are the genic and phenotypic variances at the limit. The difference between σ_y^2 and σ_g^2 is then the variance due to linkage disequilibrium at the limit. If $\sigma_y^2(t)$ were constant, $u_y(t)$ would converge geometrically to $u_y(\infty)$ (see (2.14)), but the process is modified by the decline of $\sigma_y^2(t)$ from $\sigma_y^2(0)$ to $\sigma_y^2(\infty)$, which will bring about a corresponding decline in the rate of convergence.

4.2.4. *Mutation*

Up to this point we have not considered the effect of mutation, as a source of introducing fresh variability, on the long-term response.

The evidence of new variation from mutation in selected lines in the laboratory has been reviewed by Frankham (1980). Hill (1982a,b) developed a theory to predict response to artificial selection from new mutation in a small population. In chapter 3 we considered the maintenance of genetic variability at the selection limit in terms of mutation-selection balance. Here we consider the effect of mutation on the long-term response in a large population.

Let $\sigma_m^2(t)$ be the variance from mutation at generation t, and $\Delta\sigma_m^2$ be the contribution to the variance from newly arisen mutants each generation which will be assumed to be constant. Then we may write

$$\sigma_m^2(t)=\Delta\sigma_m^2+\Delta\sigma_m^2(1)+\ldots+\Delta\sigma_m^2(t-1),$$

where $\Delta\sigma_m^2(t)$ is the variance arising from mutation t generations ago that is still present in the population. In a large population one would expect $\Delta\sigma_m^2(t)$ to decline gradually with time as a consequence of selection. So the change of $\Delta\sigma_m^2(0)$ in subsequent generations appears to be important in determining the process of accumulation of variance from mutation. There are, however, some problems in discussing the change in $\Delta\sigma_m^2(t)$. In an experiment the parameters that can usually be observed are the variance increase from mutation per generation ($\Delta\sigma_m^2$) and/or the total variance from mutation ($\sigma_m^2(t)$). It is impossible to pursue the change of $\Delta\sigma_m^2(0)$ in subsequent generations, because the new variance is combined with that existing previously in the population. So the theoretical change in $\Delta\sigma_m^2(t)$ can not be measured experimentally. Also the change in $\Delta\sigma_m^2(t)$ would be expected to depend on the value of $\sigma_m^2(t)$. If, however, every mutation is assumed to occur at a different site on the chromosomes since repeated occurrences of the same mutation in

the same population are unlikely, the change of $\Delta\sigma_m^2(0)$ in subsequent generations could be regarded independently of $\sigma_m^2(t)$ (ignoring linkage). The current mean of the population would influence the change in $\Delta\sigma_m^2(t)$ as well. It would be expected that mutation generates more negative mutants than positive ones as the selection limit is approached. Hence, the variance arising near the limit might change in subsequent generations in a different way from the variance arising in the initial stage of experiments. But here we will assume that the change in $\Delta\sigma_m^2(t)$ is unaffected by the change of the population mean and also variance. Thus we regard the change of $\Delta\sigma_m^2(0)$ in subsequent generations as an independent consistent deterministic process. It appears that this process could be best described as an exponential one. That is, we assuming

$$\Delta\sigma_m^2(t)=e^{-\lambda t}\Delta\sigma_m^2, \tag{4.50}$$

where λ is the rate of decay which would be expected to be a function of mutant effects and intensity of selection (in a small population it should be a function of effective population size as well). Then,

$$\sigma_m^2(t)=\sum_{i=0}^{t-1}\Delta\sigma_m^2(i)=\sum_{i=0}^{t-1}e^{-\lambda i}\Delta\sigma_m^2,$$

and $$\sigma_m^2(\infty)=(1-e^{-\lambda})^{-1}\Delta\sigma_m^2\approx\lambda^{-1}\Delta\sigma_m^2. \tag{4.51}$$

Usually, $\Delta\sigma_m^2$ is defined as

$$\Delta\sigma_m^2=2\sum_{i=1}^{n_m}\mu_i\alpha_i^2, \tag{4.52}$$

where μ_i is the mutation rate for the ith mutant, α_i is its effect on the quantitative character and n_m is the number of newly arisen mutants in the population. The quantity $\sigma_m^2(\infty)$ is the equilibrium

genetic variance with mutation-selection balance, which has been shown to be

$$\sigma_m^2(\infty) \approx 4n_m\mu\sigma_x^2(\omega^2+\sigma_x^2)/[\sigma_x^2+\iota(\iota-Z)\omega^2]$$

for stabilizing and truncation selection with infinite population size under the condition of $\mu_i \leq 10^{-4}$ from (3.23). Therefore,

$$\lambda=\alpha^2[\sigma_x^2+\iota(\iota-Z)\omega^2]/[2\sigma_x^2(\omega^2+\sigma_x^2)], \tag{4.53}$$

where α is the averaged absolute value of mutant effects on the character.

Equation (4.44) can then be written as

$$\sigma_y^2(t+1)=\sigma_g^2(t)+\Delta\sigma_g^2+(1/2)\sigma_d^2(t)+(1/2)\Delta\sigma_d^2+\sigma_m^2(t)+\Delta\sigma_m^2. \tag{4.54}$$

Numerical examples of the effect of mutation on the long-term response under this model will be given in the next section.

4.3. Limits to Selection

4.3.1. *Concept of limits*

In any long-term selection experiment, the response to selection cannot be expected to continue indefinitely. Sooner or later it is to be expected that the rate of response reduces to zero. When the response has ceased the population is said to be at a selection limit. Generally speaking, the cessation of response can be attributed to two causes: the exhaustion of genetic variance, *i.e.*, $h^2=0$, and the decline of the effective selection differential, *i.e.*, $s=0$. The former can result from the fixation of all the relevant genes in the population and the latter can be brought about by some balance of forces, such as the conflict between natural and

artificial selection as considered in this thesis.

Here for the convenience of discussion, let us denote L_h as the possible limit caused by fixation of the genes segregating in the base population (ignoring mutation effects), and L_s as the limit due to decline in selection differential. Then if $L_s < L_h$, a limit to selection will be reached where $s=0$; otherwise, if $L_s > L_h$, L_h will be obtained in the absence of mutation. However, if we take mutation into account, the population will pass through L_h and continue to respond to selection from the fresh genetic variance introduced continuously by mutation, until finally it stops at L_s in the case of $L_s > L_h$. So, in this sense, L_s is the limit we might observe in large populations. But, since the conclusion is drawn from the assumption of infinitely large population size, this does not rule out the possibility that a temporary plateau could be reached due to $h^2=0$ in a small population, as has clearly been indicated by some experiments (e.g., Falconer and King, 1953; Brown and Bell, 1961; Roberts, 1966). Because the values of L_h and L_s depend on many factors, they are not easy to quantify. However, if all the genes are additive with initial frequencies 0.5, a simple approximation for L_h could be

$$L_h = \sum_{i=1}^{n} a_i , \tag{4.55}$$

from (4.40), and if the distribution is normal,

$$L_s = (\iota/\sigma_x)\{\omega^2(\sigma_x^2+\omega^2)\}^{1/2} , \tag{4.56}$$

from (4.48), expressed as deviation from the optimum value in units of phenotypic standard deviation in the base population.

Distinguishing L_s from L_h has another advantage in the theoretical discussion. In the case that $L_s > L_h$, the maintenance of genetic variance at the limit (L_s) will mainly be determined by the balance between mutation and selection, as discussed in chapter 3. While, if $L_s < L_h$, some of the genetic variance in the base population will still be present in the population at the limit. So the genetic variance at this kind of limit will be expected to be higher than the prediction based on the mutation-selection balance.

4.3.2. *Distribution at the limits*

4.3.2.1. *Case I:* $L_s < L_h$

Let us consider first the case of $L_s < L_h$. A numerical example is shown in Fig.4.1 which illustrates the process of distribution change expressed in mean, variance, skewness and kurtosis with the infinitesimal model, starting with a normal distribution. Another example shown in Fig.4.2 is with the n-locus model. For simplicity, all relevant measurements in the figures and table are expressed in units of phenotypic standard deviation in the base population, $\sigma_x(0)$. The mean gene frequency starts at 0.5 and the initial genetic variances are taken to be 0.5 as well in all the examples.

It can be seen from Fig.4.1 that the linkage disequilibrium effect on skewness and kurtosis is very small, less than 0.02 and 0.004 respectively, following a pattern of increasing in the first generation and then decreasing to approach the equilibrium values. This kind of result has also been observed in different computations

with some other values of the parameters P and w^2. So truncation introduces little divergence from normality through generating linkage disequilibrium (ignoring gene frequency change), essentially because of the balance between random mating and selection. This is also true even with non-Gaussian initial distributions.

However, when gene frequency change is taken into account, the distribution will become a little more positive skew and leptokurtic (Fig.4.2). As a consequence, the limit obtained is smaller than that approximated by the normal distribution approach, by an amount 0.05 ~ 0.2 $\sigma_x(0)$, depending on the mean gene frequency at the limit (*i.e.*, the difference between L_s and L_h), which determines the skewness and kurtosis of the distribution (the upper part of Table 4.1).

4.3.2.2. *Case II:* $L_s > L_h$

When $L_s > L_h$, the response in the late period of selection will depend greatly on the variance introduced by mutation. Fig.4.3 is an example which shows the effect of mutation on long-term response (with the general approach). As expected, the response ceases at L_h, when $\Delta\sigma_m^2=0$, and continues until the mean reaches L_s in the presence of mutation.

Since the third and fourth cumulants of the distribution are mainly determined by the components of the gene frequency (k_{3g} and k_{4g}), which are proportional to the genic variance (σ_g^2) (see (4.40)), the skewness and kurtosis of the distribution at the limit could then roughly be estimated from σ_m^2 which is mainly responsible for the

genic variance at the limit. For example, taking $\Delta\sigma_m^2=0.005$, $\alpha^2=0.1$ and $\mu=10^{-4}$ gives $n_m=250$, and if $\omega^2/\sigma_x^2=8$ and $P=0.3$, the equilibrium genetic variance from mutation, σ_m^2, is calculated to be 0.133. That would then give the average frequency of mutants, q_m, about 0.0027 and skewness and kurtosis roughly 0.872 and 0.757 respectively from (4.41). In this calculation the number of mutants is fixed to that occurred in the first generation. Mutation in subsequent generations simply increases the frequencies of the mutants but selection reduces them. An alternative approximation could be obtained by taking $n_m=250\lambda^{-1}=6533$, if we assume that every mutation creates a new mutant and mutation simply increases the number of mutants but selection reduces it, in which case $q_m=10^{-4}$. This gives $\gamma_{3g}=0.875$ and $\gamma_{4g}=0.765$, which are just about same as the estimates of 0.872 and 0.757. These approximations are subject to the conditions that the gene effects and frequencies are the same for all the mutants. If the mutant effect, α, varies among the different loci, the approximations given here tend to underestimate the skewness and kurtosis. However, the effect of variation in gene frequencies among the mutants is to reduce values of predictions. So variation in gene frequencies and effects tends to cancel each other out to leave the approximations roughly unaffected (O'Donald, 1971). With this order (about 1) of values of the skewness and kurtosis, the Gaussian approximation could seriously overestimate the limit (the lower part of Table 4.1).

Table 4.1

Different approaches for the estimation of genotypic distribution at the limits to selection (with mutation), with $\Delta\sigma_m^2=0.005$ and $\alpha^2=0.1$. The upper part shows the limits for case I, *i.e.*, $L_s < L_h$, and the lower part for case II, *i.e.*, $L_s > L_h$.

n	a	P	ω^2		u_y	σ_y^2	$t_{0.5}$ †	γ_{3y}	γ_{4y}
50	0.1414	0.5	5	General	4.55	0.344	10	0.160	0.012
				Gaussian	4.73	0.330	11	—	—
100	0.1000	0.3	5	General	6.83	0.308	11	0.126	0.009
				Gaussian	6.98	0.300	11	—	—
200	0.0707	0.5	10	General	8.84	0.359	19	0.085	0.005
				Gaussian	9.00	0.352	19	—	—
400	0.0500	0.2	8	General	12.92	0.319	16	0.065	0.003
				Gaussian	13.00	0.317	17	—	—
50	0.1414	0.1	5	General	10.79	0.106	12	1.309	1.116
				Gaussian	11.94	0.104	16	—	—
100	0.1000	0.3	8	General	10.56	0.119	16	1.234	1.033
				Gaussian	12.25	0.117	21	—	—
200	0.0707	0.4	13	General	14.14	0.126	26	1.183	0.975
				Gaussian	16.24	0.126	32	—	—
400	0.0500	0.2	15	General	24.14	0.115	32	1.258	1.073
				Gaussian	27.36	0.112	39	—	—

† $t_{0.5}$ stands for the generation number to reach a half of total response.

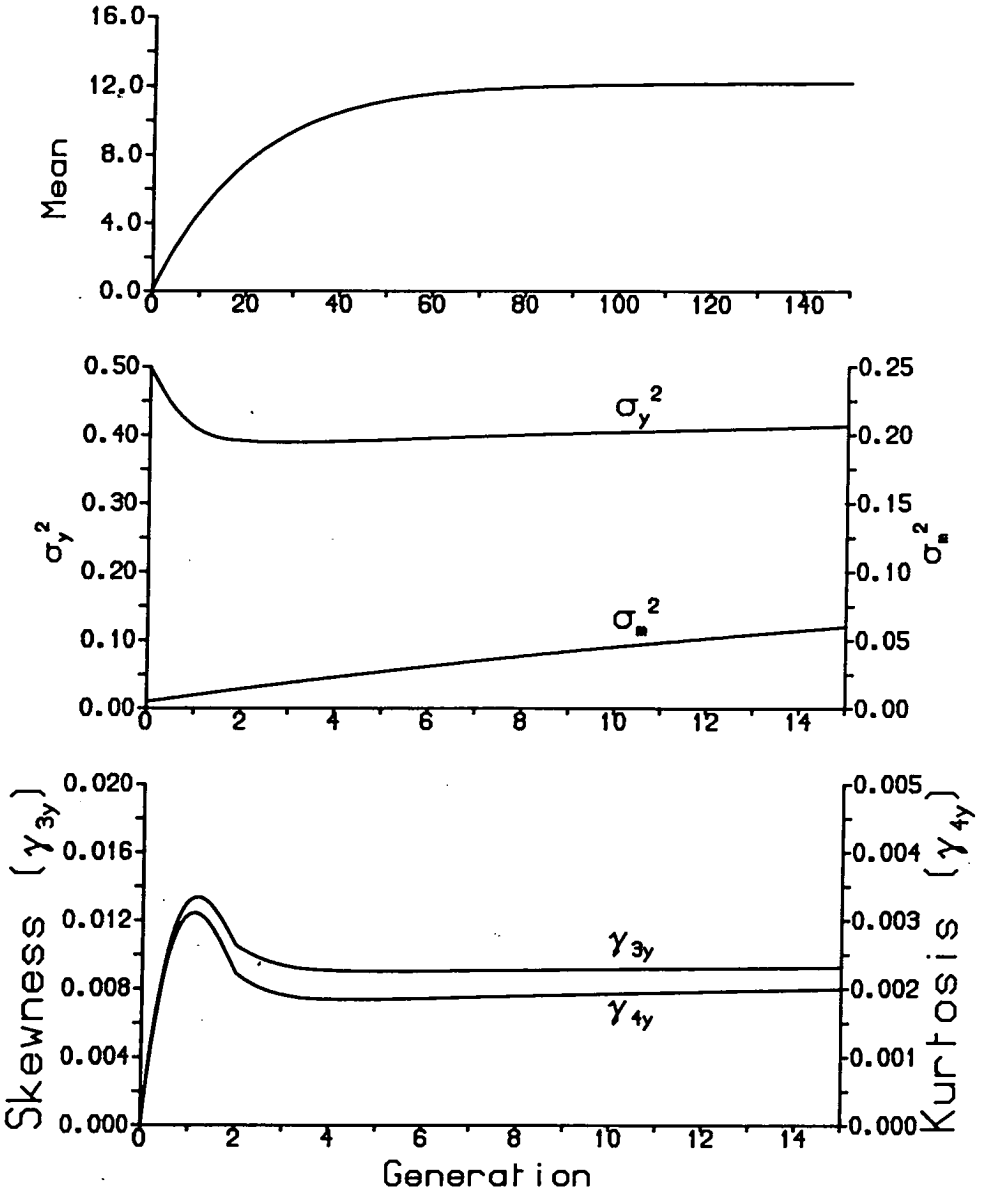

Fig.4.1: An example of change in genotypic distribution under long-term stabilizing and truncation selection, expressed in mean (u_y), variance (σ_y^2), skewness (γ_{3y}) and kurtosis (γ_{4y}) with the infinitesimal model, starting with a normal distribution. The intensity of stabilizing selection (ω^2) is taken to be 8, and the truncated proportion (P) is 0.2. The effect of mutation is included with $\Delta\sigma_m^2=0.005$ and $\alpha^2=0.1$.

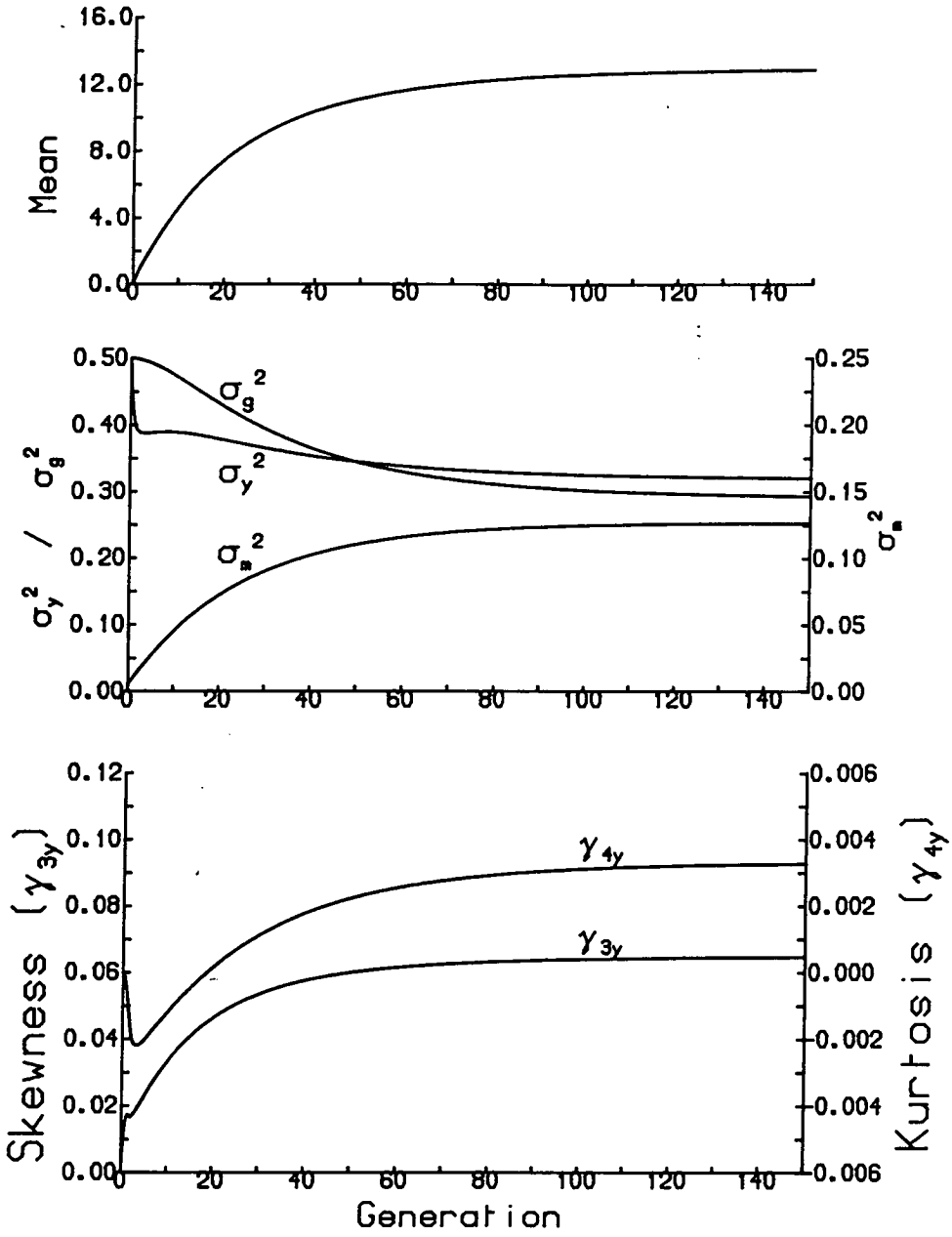

Fig.4.2: A similar example as in Fig.4.1, but with the n-locus model. The number of loci (n) is 400, and the average effect of gene substitution (a) is 0.05. Other parameters are the same as in Fig.4.1.

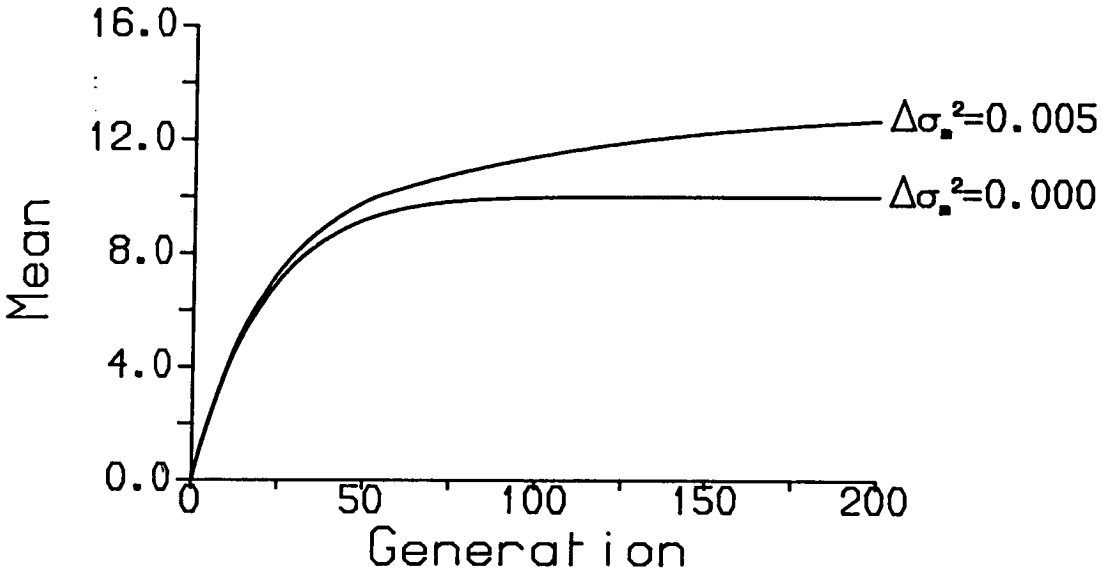

Fig.4.3: Effect of mutation on long-term response with n=100, a=0.1, ω^2=10, P=0.3, $\Delta\sigma_m^2$=0.005 and α^2=0.1. A response curve with $\Delta\sigma_m^2$=0 is drawn for comparison.

4.4. Discussion

It is now clear that the effect of truncation selection in introducing departures from normality is mainly through the change of underlying gene frequencies, driving them towards extreme values, rather than through the generation of linkage disequilibrium. So the shape of the genotypic distribution is essentially determined by the gene frequency components (k_{3g} and k_{4g}). Raff (1950) has shown that if $2nq^{3/2} > 1.07$, the error in using the normal distribution function instead of the binomial never exceeds 0.05. Therefore the Gaussian approximation tends to be appropriate when the mean gene frequency is not very extreme, say in the range 0.05 to 0.95, and the number of loci is not small, say over 50, regardless of the type of selection in operation. Otherwise, the approximation can perform poorly, especially in the neighbourhood of the selection limits (in case II).

It appears that the above conclusion remains approximately unaffected by variation in gene frequencies and effects among loci (O'Donald, 1971), unless the greater part of the genetic variance is due to genes of large effect at extreme frequencies. The case of a few major genes accounting for a large proportion of genetic variance is not uncommon for some characters, such as bristle numbers in *Drosophila*, and has quite frequently been revealed by experiments (*e.g.*, Clayton and Robertson, 1957; Yoo, 1980b; Gallego and Lopez-Fanjul, 1983). The frequencies of these major genes are likely to move towards extreme values much more quickly than those of a great many minor ones in the course of directional selection, so that a great proportion of initial responses in the experiments is

sometimes attributed to the gene frequency changes of these major genes (Gallego and Lopez-Fanjul, 1983). In consequence, the genotypic distribution could become skew in short-term selection. Unfortunately, there has been no investigation in selected populations (as far as I know) along the lines of the study in an unselected population by Hammond and James (1970) to detect the genes of large effect using the third and fourth cumulants of the genotypic distribution.

To clear up the role of mutation on the long-term response, it is necessary to evaluate the time scale of the accumulation of the genetic variance from mutation. This can be shown by considering the 'half-life' of the process for the accumulation, the time needed to reach a half of the equilibrium value, which turns out to be $\lambda^{-1}\ln 2$ generations with infinite population size (where λ is the rate of decay of the variance from newly arisen mutation in subsequent generations (4.53)), *e.g.*, 18 generations for $\alpha^2=0.1$, $\omega^2/\sigma_x^2=8$ and $P=0.3$. This is not a short time in practice with animals. In a theoretical study of selection response from new mutations, Hill (1982b) showed that for populations with intermediate sizes at least 20 generations or so would be needed for mutations to accumulate for selection to be very effective. The present calculation supports this argument.

The effect of mutation on the long-term response and limit to selection is quite complicated. It depends on the relative values of different parameters *i.e.*, L_s and L_h. In the case of $L_s < L_h$, mutation actually decreases long-term response rather than increasing

it, although it slightly increases short-term response. The reason is that when $L_s < L_h$, the restriction for long-term response is on selection differential and L_s is inversely proportional to σ_x^2. As σ_x^2 is increased by mutation, the limit is slightly decreased. However, when $L_s > L_h$, mutation plays a central role in long-term response, as it supplies fresh variability to break through L_h, the cases which have been shown as examples in Fig.4.3 and Table 4.1 (the lower part).

In judging the use of the Gaussian approximation, we have to consider the time scale of selection experiments in practice. Typical selection experiments with farm and experimental animals are usually less then twenty generations or so. For this duration, a `plateau' might be indicated, but the distribution may not be very skew (except for the possible major gene events). We might then find that during the course of selection the Gaussian approximation could serve as a simple way of predicting further response, using estimated parameters, and such an approximation might be useful and even reliable, if estimated parameters are reliable. So equations (4.46), (4.47), (4.48) and (4.49) might have some potential use.

The limitations of this analysis are obvious since the model assumes additive genes with an independently normally distributed environmental effect. So any complication in the relationship of effects between the alleles and loci, such as dominance, epistasis and linkage, would cause departures from the simple theory for prediction of the long-term response. Some of these omissions can be taken into account by some special examinations on these effects,

such as directional dominance (Fisher, Immer and Tedin, 1932), and linkage effect on the genetic variance (Bulmer, 1974); but usually these effects are unpredictable. Moreover, the nature of environmental, or non-additive genetic, effects is usually unknown for the characters examined in the experiments. Their masking effects may not seriously bias the prediction of response (Clayton, Morris and Robertson, 1957), but the shape of the genotypic distribution is highly unpredictable for the characters with low heritability (Hammond and James, 1970; Hammond and James, 1972).

Finite population size will greatly complicate the problem. If the population is not very small, the selection limit will not normally be influenced by the population size especially when stabilizing selection is strong and mutation is sufficient to maintain the genetic variance. But if we consider the influence of fitness reduction and inbreeding depression in a small population, the response will still depend on population size, and the accumulation of the variance from mutation is also proportional to population size. Detailed discussion of population size on various aspects of long-term responses has been given by Hill (1986, references therein).

Summing up, the analysis supports the use of the Gaussian approximation for the distribution of the total genetic effects (the genotype) even under long-term continuous selection. The degree of departure from normality is mainly determined by the number of loci and gene frequencies and is unlikely to be high for the quantitative characters controlled by multiple genes. So the process of the

long-term response tends to be predictable for populations with large size, but the predictions could seriously be biased by the major gene events in a small population, which are highly unpredictable.

4.5. Summary

A general procedure for analysing the change of genotypic distributions under stabilizing and truncation selection is described in this chapter and used to investigate the genotypic distribution at the limits to selection. For comparison, a simple approximate procedure using a normal distribution is also presented. It is clear that in the long term truncation introduces departures from normality mainly through gene frequency change, rather than through the generation of linkage disequilibrium under random mating. With additive gene effects the Gaussian approximation performs reasonably well for predicting the response to selection unless the mean gene frequency is very extreme (say, outside the range of 0.05 to 0.95) and the number of loci is small (say, less then 50) regardless of the type of selection in operation. The genotypic distribution at the limits to selection largely depends on the type of limit reached. If a limit is obtained due to the action of natural selection before exhaustion of the original genetic variation, the distribution will normally not be very skew, but if a limit is reached at which mutation plays a central role in the maintenance of genetic variability, it could have high coefficients of skewness and kurtosis. The role of mutation on the long-term response is also discussed.

CHAPTER 5

MULTIVARIATE SELECTION: STABILIZING COADAPTATION

5.1. Introduction

Selection does not occur on single characters in isolation; many characters together affect the success and failure of an individual. In nature different characters of organisms are usually coadapted to the environment. The phenomena of coadaptation between characters in evolution are so intricate that there must be many causal mechanisms involved. Among the known mechanisms that can produce correlated change in different characters of the same organism are genetic correlation, ontogenetic (or physiological) interdependence and functional interaction (Simpson, 1953, p.275). Not all correlated changes are adaptive, but the following discussion of coadaptation is restricted to those correlated changes which are adaptive. It has been suggested that the coadaptation between characters could be explained as a consequence of genetic correlation between the characters together with multivariate selection and random genetic drift (Lande, 1979). However, a close examination of some evolutionary phenomena reveals some difficulties with this explanation.

There are several examples of differences in the magnitude and sign of the correlation between coadapted characters when considered within species or between taxa. Lande's (1979) quantitative genetic analysis of brain:body size allometry showed the estimated brain:body allometry $\alpha = 0.36$ from directional selection only on body size in mice

which differs considerably from α near 0.67 observed for interspecific data among large taxonomic groups (Jerison, 1973; Gould, 1975). Atchley (1984) has also observed in his experiment on rats that the brain:body allometry of females within a taxon differs significantly from that between taxa. It thus appears that the relationship between brain size and body size within populations does not hold between populations.

Another more striking example is the relationship between body weight and litter size in mammals. It has been confirmed that there is a general tendency for average litter size to decrease with increasing body weight across species in mammals (May and Rubenstein, 1984, p.10). However, within a species (at least in mice) high litter size tends to be associated with high body weight and *vice versa* (Land, 1984, p.67), exactly the opposite to the relationships observed between species. These discrepancies can somehow hardly be explained by the genetic correlation hypothesis.

It has long been thought that natural selection for adaptation is probably a compound of two phenomena —— one directive, and the other stabilizing. The first is the classical form leading to the transformation of a population by shifting its mean properties. The second refers to the tendency for a population to remain stable, or genetic homeostasis (Schmalhausen, 1949; Simpson, 1953; Lerner, 1954). Since the early work of Bumpus (1899) on the house sparrow and Weldon (1901) on the land snail, many examples of stabilizing selection have been reported. If stabilizing selection in favour of an optimal combination of phenotypes is one of the common selection

forces in natural populations, it can be imagined that any environmental change which would lead populations towards new adaptation would be countered and balanced by the existing stabilizing selection. The process of adaptation of a population to its environment may therefore be considered to be a resultant or compromise between stabilizing and directive components of natural selection.

In this chapter, the effect of the interplay between stabilizing and directional selection on the adaptation and coadaptation of quantitative characters is examined. First, a multivariate analysis is given, using standard quantitative genetic methods. The result of this analysis shows that the responses of characters to selection in the short term differ qualitatively from those in the long term. In the short term the responses depend on genetic correlations between characters as expected, but in the long term they are determined only by the fitness functions of stabilizing and directional selection, independent of genetic correlations and also phenotypic correlations. Then, based on this contra-intuitive result, it is argued that genetic correlation might not be really responsible for the coadaptation between characters in evolution, instead a parameter of the fitness function of stabilizing selection, the "coadaptive coefficient", might be the link between the adaptations of different characters.

5.2. Multivariate Analysis

A common assumption in multivariate analysis of inheritance is that both phenotypes and genotypes of quantitative characters follow multinormal distributions, an assumption made in this analysis also. This is essentially based on the Central Limit theorem that as the number of factors influencing genotypes as well as phenotypes increases, the distributions approach multinormal. For quantitative characters controlled by multiple genes, the assumption of normality is usually satisfied, at least approximately, after some appropriate scale transformation (Wright, 1968).

The form of directional selection formulated is of truncation, as practised in animal and plant breeding. Although in nature directional selection is surely not so sharp on the cut-off point as in truncation, the consequences on the change of mean and variance due to selection are similar for different types of directional selection except for differences in intensity. So the generality of the results should not be restricted by the assumption of truncation (see chapter 6).

Let x be a column vector of phenotypic measurements of n quantitative characters and suppose that the corresponding vectors of additive genetic effects, y, and environmental deviations, e, follow independent multivariate normal distributions with $x=y+e$, so that the probability density functions of y and e are

$$g(y)=(2\pi)^{-n/2}|G^{-1}|^{1/2}exp\{-(1/2)(y-u_y)^T G^{-1}(y-u_y)\} \qquad (5.1)$$

$$h(e)=(2\pi)^{-n/2}|E^{-1}|^{1/2}exp\{-(1/2)(e-u_e)^T E^{-1}(e-u_e)\}$$

where the genetic and environmental covariance matrices, G and E, are assumed to be non-singular and $u_e=0$. The superscript ^{T} denotes

transposition. The distribution of x is then also multivariate normal with mean $u_x=u_y$ and covariance matrix $P=G+E$,

$$f(x)=(2\pi)^{-n/2}|P^{-1}|^{1/2}exp\{-(1/2)(x-u_x)^TP^{-1}(x-u_x)\}. \quad (5.2)$$

The assumption of a joint multivariate normal distribution of x and y implies that the regression of genetic effects on phenotypes is linear and homoscedastic with

$$E(y|x)=u_y+GP^{-1}(x-u_x) \quad (5.3)$$

and $Var(y|x)=(I-GP^{-1})G$

where I is the identity matrix.

A well-known result due to Pearson (1903) is that selection on x does not influence the regression of y on x (5.3). So the change on y due to selection on x can be inferred from the regression. In the following analysis, we shall first examine the change in x due to stabilizing selection followed by truncation selection. From (5.3) we then determine the change in y due to selection on x. Finally, we complete the analysis of a life cycle by determining the transmission from parents to offspring, using the infinitesimal model.

5.2.1. *Selection*

Stabilizing selection which acts on the phenotypes is taken to be a Gaussian function

$$w(x)=exp\{-(1/2)(x-\theta)^TW^{-1}(x-\theta)\}, \quad (5.4)$$

where W is a positive definite symmetric matrix and θ is the optimum vector which will be taken to be zero for every element. The matrix W is a measure of intensity of stabilizing selection. The diagonal

elements, ω_{ii}, of W approximate the strength of stabilizing selection acting directly on each character, the higher values of ω_{ii} reflect the weaker stabilizing selection; whereas the off-diagonal elements, ω_{ij} $(i \neq j)$, approximate the strength of stabilizing selection acting on different characters jointly, which will be shown to determine the correlated responses to the selection in the long term (*cf.* Lande and Arnold, 1983; Lande, 1984).

With (5.2) and (5.4) the distribution of x after stabilizing selection has the density function

$$f'(x) = f(x)w(x) / \int f(x)w(x)dx \qquad (5.5)$$

which is still multivariate normal. The denominator of the right side of (5.5) is a constant. The mean vector u_x' and covariance matrix P' of $f'(x)$ can be found from

$$P'^{-1} = P^{-1} + W^{-1}$$

and $$P'^{-1}u_x' = P^{-1}u_x + W^{-1}\theta$$

by equating like terms in (5.5), which give $u_x' = W(W+P)^{-1}u_x$ and $P' = W(W+P)^{-1}P$, since $\theta = 0$.

Now we consider truncation selection. Truncation selection usually takes a form that those individuals above a certain criterion, τ, will be saved for reproduction and those below τ will be discarded. The criterion τ could be set up on a particular character (single character truncation), or on an index in a linear combination of multiple characters (index truncation). Both procedures have frequently been used in artificial selection programmes and are also believed to be common in nature (e.g., Lande and Arnold, 1983).

We first consider single character truncation for simplicity. Suppose that a fixed proportion (P) of individuals with highest value on one character, say x_1, is selected for reproduction in each generation. Then after truncation the means of the characters become

$$u_i^* = u_i' + \sigma_{1i}' \iota / \sigma_1' \qquad (i=1,\ldots,n), \tag{5.6}$$

where σ_{1i}' is the covariance between x_1 and x_i after stabilizing selection but before truncation selection, being the element in the matrix $\mathbf{P}'$, $\sigma_1' = \sqrt{\sigma_{11}'}$ and ι is the intensity of truncation selection. The variance of x_1, after truncation, is known to be $\sigma_{11}^* = \sigma_{11}'(1-\iota(\iota-Z))$ (4.15), where Z is the standard deviate of the truncation point τ. Thus by using the result of Aitken (1934), we have the following expression for the variances and covariances of the x_is after truncation selection

$$\sigma_{ij}^* = \sigma_{ij}' - \sigma_{1i}'\sigma_{1j}'\iota(\iota-Z)/\sigma_{11}' \qquad (i,j=1,\ldots,n). \tag{5.7}$$

If truncation is on an index, I, constructed for a linear combination of the first m characters, $m < n$,

$$I = \mathbf{b}^T\mathbf{x}$$

where $\mathbf{b}^T=[b_1,\ldots,b_m,0,\ldots,0]$, and b_i is the index coefficient of the ith character, the means of the characters, after truncation, are then

$$u_i^* = u_i' + \sum_{r=1}^{m} b_r \sigma_{ir}' \iota / \sigma_I' \qquad (i=1,\ldots,n) \tag{5.8}$$

where $\sigma_I' = \sqrt{[\mathbf{b}^T\mathbf{W}(\mathbf{W}+\mathbf{P})^{-1}\mathbf{P}\mathbf{b}]}$ is the standard deviation of the index, and the variances and covariances of the x_is are

$$\sigma_{ij}^* = \sigma_{ij}' - \sum_{r=1}^{m} b_r \sigma_{ir}' \sum_{r=1}^{m} b_r \sigma_{jr}' \iota(\iota-Z)/\sigma_{II}' \qquad (i,j=1,\ldots,n). \tag{5.9}$$

Equations (5.6) and (5.8) can be expressed in matrix notation as

$$\mathbf{u}_x^* = \mathbf{W}(\mathbf{W}+\mathbf{P})^{-1}\mathbf{u}_x + \mathbf{W}(\mathbf{W}+\mathbf{P})^{-1}\mathbf{P}\mathbf{a} \qquad (5.10)$$

with $\mathbf{a}^T=[1,0,\ldots,0]\iota/\sigma_1'$ for single character truncation, and $\mathbf{a}^T=[b_1,\ldots,b_m,0,\ldots,0]\iota/\sigma_I'=\mathbf{b}^T\iota/\sigma_I'$ for index truncation. The deviation $\mathbf{u}_x^*-\mathbf{u}_x$ is called the selection differential vector. Similarly, for (5.7) and (5.9) the matrix notation is

$$\mathbf{P}^* = \mathbf{W}(\mathbf{W}+\mathbf{P})^{-1}\mathbf{P} - \mathbf{W}(\mathbf{W}+\mathbf{P})^{-1}\mathbf{P}\mathbf{b}\mathbf{b}^T\mathbf{W}(\mathbf{W}+\mathbf{P})^{-1}\mathbf{P}c \qquad (5.11)$$

with $\mathbf{b}^T=[1,0,\ldots,0]$, $c=\iota(\iota-Z)/\sigma_{11}'$ for single character truncation, and $\mathbf{b}^T=[b_1,\ldots,b_m,0,\ldots,0]$, $c=\iota(\iota-Z)/\sigma_{II}'$ for index truncation.

It follows immediately that the means and covariances of y after all selection are

$$\begin{aligned}\mathbf{u}_y^* &= E[E(\mathbf{y}|\mathbf{x})] \\ &= \mathbf{u}_y + \mathbf{G}\mathbf{P}^{-1}[\mathbf{W}(\mathbf{W}+\mathbf{P})^{-1}(\mathbf{u}_x+\mathbf{P}\mathbf{a})-\mathbf{u}_x] \qquad (5.12)\end{aligned}$$

$$\begin{aligned}\mathbf{G}^* &= E[E(\mathbf{y}|\mathbf{x})^2-\mathbf{u}_y^{*2}]+Var(\mathbf{y}|\mathbf{x}) \\ &= \mathbf{G}\mathbf{P}^{-1}\mathbf{P}^*\mathbf{P}^{-1}\mathbf{G}+(\mathbf{I}-\mathbf{G}\mathbf{P}^{-1})\mathbf{G} \\ &= \mathbf{G}-\mathbf{G}\mathbf{P}^{-1}(\mathbf{I}-\mathbf{P}^*\mathbf{P}^{-1})\mathbf{G} \qquad (5.13)\end{aligned}$$

from (5.3), (5.10) and (5.11).

5.2.2. *Transmission*

Bulmer (1980) has showed that if the controlling factors for a quantitative character are numerous, the change in the genetic variance caused by selection must be mostly due to the build-up of linkage disequilibrium and such a change is then only temporary and will be restored after selection is relaxed (the so called infinitesimal model). This also holds for the genetic covariance between two characters if the factors influencing two characters are

effectively infinite. So if we extend Bulmer's analysis to the case of multiple characters, we have

$$\mathbf{u}_y(t+1)=\mathbf{u}_y^*(t) \tag{5.14}$$

$$\mathbf{G}_{t+1}=(1/2)\mathbf{G}_t^*+(1/2)\mathbf{G}_0 \tag{5.15}$$

in the absence of sexual dimorphism and with random mating, where $\mathbf{u}_y^*(t)$ is the vector of means of y after selection in generation t, $\mathbf{u}_y(t+1)$ is the vector of means of y before selection in the next generation, and $\mathbf{G}_0$ is the equilibrium genetic covariance matrix in the absence of selection, assumed to be positive definite. Suppose that the assumption of multivariate normal distributions of y and x holds for every generation before selection and that there is no change in the distribution of environmental deviations e across generations. Let $\mathbf{u}_x(t)=\mathbf{u}_y(t)=\mathbf{u}_t$. We then have the following recurrence relationship for the evolution of the vector of means

$$\mathbf{u}_{t+1}=\mathbf{u}_t+\mathbf{G}_t\mathbf{P}_t^{-1}[\mathbf{W}(\mathbf{W}+\mathbf{P}_t)^{-1}(\mathbf{u}_t+\mathbf{P}_t\mathbf{a}_t)-\mathbf{u}_t] \tag{5.16}$$

from (5.12) and (5.14). It is of interest to compute the response in the first generation of selection when $\mathbf{u}_0=\theta=0$. This is

$$\begin{aligned}\mathbf{u}_1&=\mathbf{G}_1\mathbf{P}_1^{-1}\mathbf{W}(\mathbf{W}+\mathbf{P}_1)^{-1}\mathbf{P}_1\mathbf{a}_1\\&=\mathbf{G}_1(\mathbf{I}+\mathbf{P}_1\mathbf{W}^{-1})^{-1}\mathbf{a}_1\\&\approx\mathbf{G}_1\mathbf{a}_1\end{aligned} \tag{5.17}$$

(see below for comparison).

Since in each generation only one-half of the variance and covariance changes due to selection are transmitted to the next generation (5.15), it is apparent that with the present model (the infinitesmal model) the matrix $\mathbf{G}_t$ will converge to an equilibrium genetic covariance matrix under selection, $\mathbf{G}_\infty$, which is unique and positive definite (see Karlin, 1979). Similarly, $\mathbf{P}_t$ will also

converge to P_∞. It should be pointed out that the existence of G_∞ and P_∞ does not, however, rely on the assumption of infinite number of factors influencing characters. There is abundant evidence to show that genetic variances and covariances of quantitative characters are not exhausted by selection in natural populations (Wright, 1978, Ch.8). The mechanism for the maintenance of genetic variances and covariances could be explained by a balance of mutation, selection and recombination (Lande, 1980). Karlin (1979) has provided a broad mathematical proof for the existence of G_∞ and P_∞. In this chapter, the infinitesimal model is used simply for illustrating the existence of G_∞ and P_∞ and for the convenience of numerical calculation. As shown later, this oversimplified assumption does not affect the following result.

Given the convergence of G_t and P_t to G_∞ and P_∞ respectively, we now determine the mean vector at the selection limit, u_∞. Let $u_{t+1}=u_t$ at the limit. Equation (5.16) gives us

$$\begin{aligned} u_\infty &= [I-W(W+P_\infty)^{-1}]^{-1}W(W+P_\infty)^{-1}P_\infty a_\infty \\ &= (W+P_\infty)P_\infty^{-1}W(W+P_\infty)^{-1}P_\infty a_\infty \\ &= Wa_\infty, \end{aligned} \tag{5.18}$$

since $G_\infty P_\infty^{-1} \neq O$, *i.e.*, the selection differential vector is zero at the selection limit. Formula (5.18) shows that the means of x and also y at the selection limit are independent of both the genetic covariance matrix G and the phenotypic covariance matrix P. They are determined only by the two kinds of selection intensities, one from stabilizing selection embodied in the matrix W, and the other from truncation selection embodied in the vector a ($a=b^T\iota/\sigma_I$). In other words, the whole complicated system of genetic and phenotypic

correlations becomes irrelevant in determining the means at the limit to stabilizing and truncation selection, although the means do depend on the **G** and **P** matrices before reaching $\mathbf{u}_\infty$.

This gives the rather surprising conclusion that the correlated responses of characters from selection depend primarily on genetic correlations in the short term (5.17), but in the long term on the influence of correlated stabilizing selection (5.18). Indeed, if stabilizing selection acts *independently* on the characters, *i.e.*, the off-diagonals, ω_{ij} $(i\neq j)$, of **W** are zero, the characters will evolve independently in the long term, even though they are correlated genetically. So the means of those characters which are not directly truncated will finally return to their original optimum values, no matter what kind of correlated responses from directional selection they have experienced previously, a situation illustrated in Fig. 5.1. But if stabilizing selection does *not* influence the characters *independently*, *i.e.*, $\omega_{ij}\neq 0$ $(i\neq j)$, as seems likely, the characters will adapt together, that is, the means of non-truncated characters will tend to respond to directional selection through the correlated influence of stabilizing selection (Fig. 5.2). The degree of coadaptation between the two characters is intrinsically determined by $\gamma_{ij}=\omega_{ij}/\sqrt{(\omega_{ii}\omega_{jj})}$, which could be called the "coadaptive coefficient".

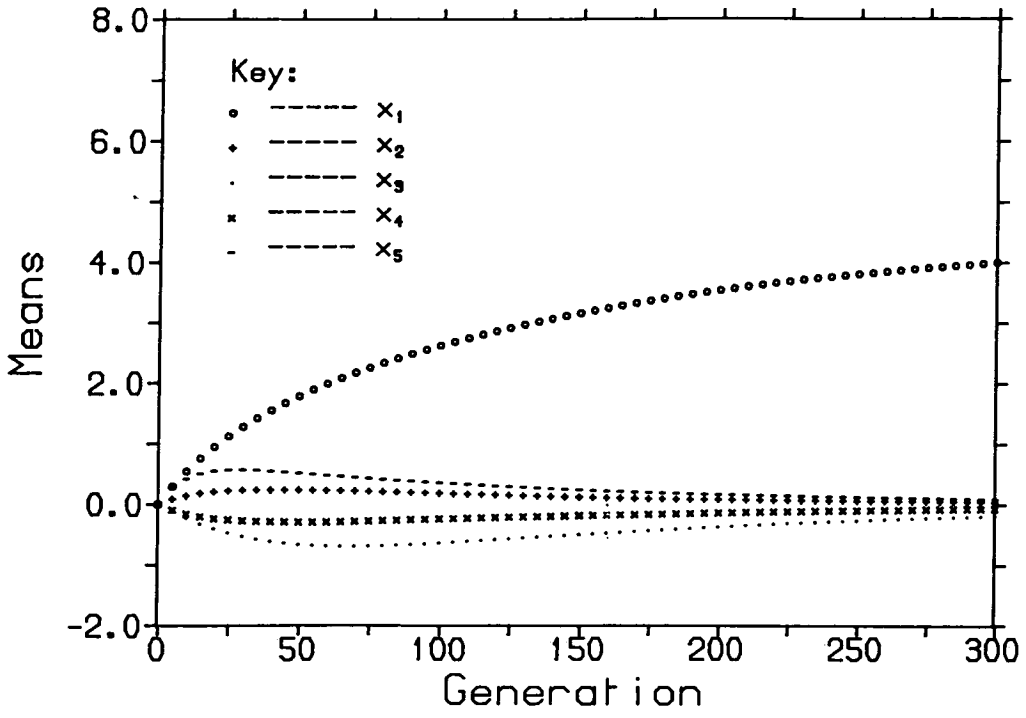

Fig. 5.1: An example of long term responses to stabilizing selection on five characters $(x_1,\ldots,x_5)$ and truncation selection on character x_1 only. The stabilizing selection is assumed to act on the five characters independently, so that $\gamma_{ij}=0$ $(i\neq j)$. The truncated proportion is 0.8, that is $\iota=0.35$ and $z=-0.824$. The base population is assumed to be at equilibrium. The parameters of the base population and the intensities of stabilizing selection are given in Table 5.1. This figure shows that $x_2,\ldots,x_5$ respond to truncation selection in the directions determined by the genetic correlations between x_1 and $x_2,\ldots,x_5$ in the short term. But in the long term they all will finally return to their original optimal values, because of the independent influence of stabilizing selection.

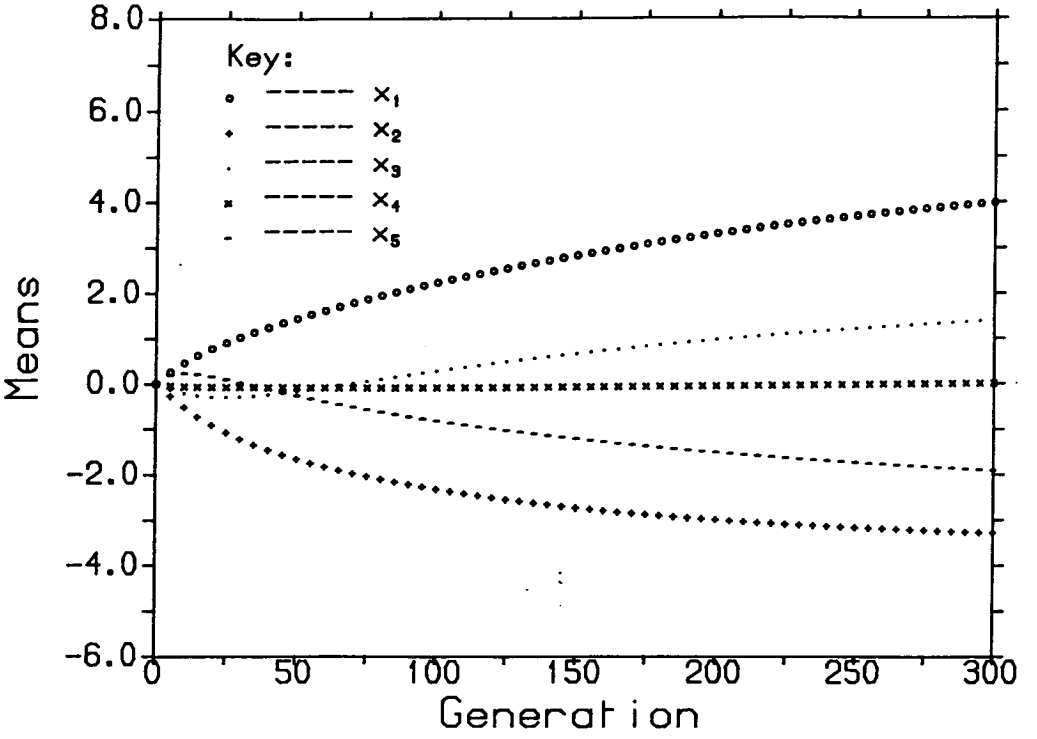

Fig. 5.2: Effects of correlated selection. The stabilizing selection on the characters in this example is not independent, and the proposed coadaptive coefficients for calculation are listed in Table 5.2. The truncation selection is on an index, $I=0.8x_1-0.1x_2$. Other parameters for the calculation are the same as in Fig. 5.1. In this example, x_1 and x_2 are under direct influence of truncation selection, so they move away from the original values and will finally approach to the selection limit (5.18). While x_3, x_4 and x_5, though not directly selected by truncation, will also move to the new equilibrium values through the correlated influences of stabilizing selection (5.18). Note that because x_3 is genetically negatively correlated with x_1 and positively correlated with x_2, the response of x_3 is negative in the short term up to about generation 50. But in the long term the response becomes positive, because the signs of the coadaptive coefficients are opposite to those of the genetic correlations. The situation of x_5 is opposite to that of x_3. There is essentially no response on x_4 in the course of selection. That is because the correlated effect of truncation selection on x_1 in changing the mean of x_4 is offset by the correlated effect of truncation selection on x_2 both in the short term and long term.

Table 5.1. Hypothetical parameters of the base population and the intensities of stabilizing selection

	σ_{ii}	$h^{2\dagger}$	w_{ii}	x_1 ‡	x_2	x_3	x_4	x_5
x_1	1.0	0.2	12.0		0.15	-0.20	-0.50	0.45
x_2	2.0	0.4	30.0	0.40		0.20	-0.40	-0.05
x_3	0.8	0.6	14.4	0.20	0.25		-0.25	0.20
x_4	0.5	0.5	5.0	-0.25	-0.35	0.05		-0.35
x_5	1.5	0.8	15.0	0.60	0.35	0.20	-0.20	

† h^2 is the heritability, *i.e.*, the ratio of genetic variance over phenotypic variance.

‡ genetic correlations are above the diagonal and phenotypic correlations are below.

Table 5.2. Parameters of coadaptive coefficients (γ_{ij})

	x_2	x_3	x_4	x_5
x_1	-0.05	0.35	0.10	-0.40
x_2		-0.25	0.20	-0.10
x_3			-0.15	-0.05
x_4				0.10

5.3. Stabilizing Coadaptation

Most organisms have some sort of homeostatic property, either genetically or physiologically, to equilibrate themselves in fluctuating environments. The tendency of populations to resist the disturbance of environment has frequently been observed in artificial selection experiments when the selection is relaxed (Lerner, 1954). However, if a selection force persists for long periods of time, the population will tend to respond to it and move to a new equilibrium; correspondingly, the optima of the characters under stabilizing selection will be moved to new locations. In natural populations, the responses from directional selection are usually adaptive for the characters directly selected. So the adaptation of quantitative characters could be viewed as the process of such a kind of movement of optima (Simpson, 1953, p.196). As the optima of the characters under the direct influence of directive selection are moved, the optima of other characters are likely also to be changed and such a correlated change of optima, as we can see from formula (5.18), is due to the coadaptive coefficients, not genetic correlations.

Based on the above argument, I suggest that correlated stabilizing selection might be the primary cause of the coadaptation between quantitative characters in evolution. This means that quantitative characters, being likely to adapt together in evolution, might essentially be determined by coadaptive coefficients between characters.

There are some technical difficulties with the concept of the

coadaptive coefficient, γ, but a geometrically conceptual explanation may help. The fitness function of stabilizing selection can be represented as a multidimensional space, similar to genetic and phenotypic frequency spaces (see (5.1), (5.2) and (5.4)). . In this space, each dimension represents the selection effect on one character. Thus, the complete space has as many dimensions as the number of characters subject to stabilizing selection, and any point on the space represents the relative fitness of individuals with the same combination of characters. The fitness effect relation between any two dimensions in this space is then quantitatively measured by γ, the "coadaptive coefficient", (statistically analogous to correlation coefficient). The magnitude of γ (just like correlation coefficient) ranges from +1 for perfect positive coadaptation to -1 for perfect negative coadaptation. When $\gamma=0$, the selection acts on the two characters independently, so that adaptation of one character does not affect adaptation of the other character.

The coadaptive coefficient is a different parameter from the genetic correlation. The comparison between intra- and interpopulation correlations of characters over time and space may give some insight about the relations and differences between genetic correlations and coadaptive coefficients. Two data sets have been produced concerning the relations between intra- and interpopulation correlations. The first data set, from a study of the geographic variation of the rabbit tick *Haemaphysalis leporispalustris* (Thomas, 1968), showed that all high intralocality correlations were associated with high interlocality correlations, while the intermediate and low level intralocality correlations could be paired

with a relatively wide range of interlocality correlations (Sokal, 1978). This pattern of relation was even more clearly observed in the other data set in the aphid *Pemphigus populitransversus* (Sokal *et al.*, 1980). This suggests that there is a close relation between intra- and interlocality correlations of the characters examined, especially when the values of intralocality correlations are high. Sokal (1978; Sokal *et al.*, 1980) suggested that the development of interlocality correlations might be circumscribed by the nature of the intralocality correlations affecting the characters concerned, so that populations tend to deviate along the principal axis of the ellipse of phenotypes. Translation of populations along the major axes of the space of fitness function, when the major axes differ considerably from those of the genetic space, requires complicated rearrangments of the genome of the population, and thus tends to be rare (Sokal, 1978). Along similar lines, Lande (1984) suggested that correlated selection might work together with some other factors, such as linkage and inbreeding, to conform genetic correlation to the shape of the fitness surface.

While recognizing the positive association between the intra- and interpopulation correlations, we should also be aware of the general discrepancies between the two kinds of correlations in the data sets. In Thomas's data, the intralocality correlations from the 64-locality study of larva were much lower than interlocality correlations from the same study. This was again supported by Sokal's data. Many authors (*e.g.*, Lande, 1979; Sokal *et al.*, 1980) thought that the origins of intra- and interpopulation correlation were basically the same, *i.e.*, mainly attributed to genetic correlations. The

discrepancies between intra- and interpopulation correlations could be explained by the likely changes of gene complexes, environmental factors and selection patterns and random drift over the time and space. The result (5.18) of this chapter, however, suggests that the basis of interpopulation correlation is coadaptive coefficient, not genetic correlation. As populations deviate from their common origin, the covariations of characters between populations will be determined by the coadaptive coefficients. Since a genetic correlation may differ from a coadaptive coefficient in magnitude and direction, the intra- and interpopulation correlations can be different. So the discrepancies between intra- and interpopulation correlations may be mainly due to the differences between the genetic correlations and the coadaptive coefficients. The relatively higher interlocality correlations over the intralocality correlations in the data suggest that the values of coadaptive coefficients might be generally higher than the averages of the genetic correlations among localities, and also indicate that coadaptive coefficients are quite stable over time and space. These might be the characteristics of the coadaptive coefficients. To confirm this, more studies are needed.

In general, there tends to be a positive association between the genetic correlations and the coadaptive coefficients of characters, especially when the values of genetic correlations are high (Thorpe, 1976; Sokal *et al.*, 1980). No doubt there must be some mechanisms which relate coadaptive coefficients to genetic correlations. However, the two parameters may differ; especially coadaptive coefficients tend to be higher than genetic correlations in

magnitude. Therefore, the differentiation of populations among coadapted characters should be interpreted on the basis of coadaptive coefficients, rather than genetic correlations.

5.4. Summary

Different parts, or characters, of an organism are usually coadapted in evolution. It has been suggested that such a coadaptation between quantitative characters could be explained by genetic correlations together with multicharacter selection and random genetic drift (Lande, 1979). There are, however, some difficulties for this explanation to interpret discrepancies between intrapopulation and interpopulation correlations of characters.

Natural selection for adaptation is more plausibly a compound of two components —— one stabilizing, and the other directive. These two component forces of natural selection are likely to oppose each other in many situations, so the process of adaptation could be conceived as a compromise between stabilizing and directional selection. A multivariate analysis of the long term effects of the interplay between stabilizing and directional selection shows that the correlated responses to selection in the long term differ qualitatively from those in the short term. Whereas in the short term the correlated responses depend on genetic correlations between characters, in the long term they are determined by the correlated effects of stabilizing selection. Based on this result, it is argued that genetic correlations might not be the main cause of the coadaptation between characters in evolution, but that a parameter of the fitness function of stabilizing selection, the "coadaptive

coefficient", might be the link between the adaptations of different characters. It is also suggested that the main origin of interpopulation correlation of characters might be the "coadaptive coefficient", not genetic correlation.

CHAPTER 6

GENERAL DISCUSSION AND CONCLUSIONS

6.1. Long term response and limit to selection

Apart from the decline in heritability which causes plateaux in some experiments (*e.g.*, Brown and Bell, 1961; Roberts, 1966), a reduction in selection differential seems to be responsible for some other limits. It has been observed that a decline in mean was rapid after relaxation of selection, and that fertility and reproductivity were much poorer in many lines —— even to the extent of causing extinction of selection lines —— in many long-term selection experiments (*e.g.*, Lerner and Dempster, 1951; Clayton and Robertson, 1957; Latter, 1966; Roberts, 1966; Wilson *et al.*, 1971; Yoo, Nicholas and Rathie, 1980). This clearly indicated that additive genetic variance was not exhausted in these populations at apparent limits and also suggested that natural selection opposing artificial selection might have caused the reduction in the effective selection differential.

In this thesis the process of long term response has been analysed in terms of a conflict between natural and artificial selection. The approach is straightforward, simply assuming natural selection acting on the phenotype in a Gaussian form towards an optimum value and artificial selection practised by truncation. It is found that in this selection model the population approaches a selection limit, determined by the intensities of stabilizing and truncation selection and the phenotypic variance (2.10), at a rate which is a function of

the intensity of stabilizing selection and heritability (2.13).

With an infinite population size the amount of genetic variance at the selection limit appears to depend on the relative intensities of the natural and artificial selection forces and also on the variance introduced by mutation (chapters 3 and 4). If artificial selection is not very strong, some alleles in the foundation population could still remain segregating in the population at the selection limit with additive gene action (chapter 4). The reduction in genetic variance due to selection could partly be compensated by mutation occurring during the course of selection. If only that part of genetic variance that is introduced by mutation is analysed, this variance is unlikely to be able to reach a high level in the face of truncation selection (chapter 3).

Normal distributions of phenotypes and genotypes have been assumed in the derivation of the simple formulae for predicting the long-term response and the limit to selection. It has been shown that the departure from normality introduced by truncation and stabilizing selection is negligible for the infinitesimal model, and also is unlikely to be high even up to the selection limit when the number of loci is not infinite, but not less than 50. Gaussian approximations generally perform reasonably well in the prediction of response during the whole course of selection, but may perform poorly near those selection limits at which the genetic variance has greatly been reduced as a result of selection.

From this study alone it is very difficult to assess the role of

mutation in long-term response. It is unlikely that mutation could make a substantial contribution to the response for at least 20-30 generations, but may afterwards. If most of the original genetic variance is depleted in the early period of selection, mutation would be mainly responsible for the further response, if any, in the late period of selection. In the present selection model the maximum response is not influenced by mutation, since the selection limit is independent of heritability. However, the limit obtained from the balance between stabilizing and truncation selection is based on an equilibrium which is very sensitive to change of intensity of selection and also to change in the relationship between fitness and the quantitative character concerned. Mutation might be able to contribute further response after a plateau seems to have been achieved.

Nicholas and Robertson (1980) analysed another natural selection model where heterozygotes at the loci affecting the quantitative character have higher fitness. Although the implications of their model to the genetic structures of population are quite different from the selection model considered in this thesis (Robertson, 1956), the two models have rather similar implications to various aspects of the long-term response process, as noted by them. Both models predict that a population might reach a selection limit while still retaining genetic variance and selection will reduce the fitness of the population, which will gradually be restored if selection is relaxed. The population mean will also be expected to move back towards the original value after the relaxation of selection and there would be a rapid response if reverse selection were practised

after the population reached a plateau. As Nicholas and Robertson (1980) observe: "In fact, there seems to be no aspect of the observable response to artificial selection that would enable anyone to distinguish between these two models of natural selection."

One direct implication of the present study is that if the character selected is influenced by many genes, each of small effect, and the population size is not small, the pattern of response to selection will tend to be repeatable and predictable, as has been demonstrated by some experiments (*e.g.*, Latter, 1966). However, many other experiments have produced quite irregular and unpredictable response patterns, which are often attributed to genes having large effects and small population size.

Effects of population size and variation in gene frequency and effects on the long-term response and variance of response have recently been examined by Hill and Rasbash (1986). They found that the shape of the distribution of gene effects was not usually important even up to the selection limit. But if genes of large effect are at low initial frequency or appear as mutants, the variance of response between replicates and between generations within replicates may be high, so the response pattern will tend to be highly unpredictable.

Various aspects of the long-term response process have been discussed in terms of the interplay between stabilizing and truncation selection. This study is, however, by no means a complete description of the process, especially because plateaux have not been

achieved in some long term selection experiments, *e.g.*, the Illinois corn experiment (Dudley, 1977), and in some other experiments the plateaux were largely achieved by selection for recessives having large effects in the heterozygotes (*e.g.*, Clayton and Robertson, 1957; Yoo, 1980b). To make the analyses more meaningful, it will be necessary to synthesize theories for predicting responses from mutation in the absence of natural selection (Hill, 1982b), the present theory incorporating stabilizing selection at the phenotypic level, and theories of natural selection acting at the genetic level through heterozygote superiority (*e.g.*, Nicholas and Robertson, 1980). Nevertheless, it is hoped that the calculations presented in this thesis may be of value in interpreting some long term selection experiments which reached a selection limit. The interpretation and prediction will be much facilitated by the simplicity and measurability of the results obtained in this thesis.

6.2. Coadaptation

Coadaptation usually means the correlated variation in mutually dependent organs, and the term has also frequently been used to describe "the evolutionary process of selection for a balanced combination of *genes* in an individual, and individuals in a population" (Lerner and Libby, 1976, p.169), a phenomenon originally discussed by Dobzhansky in his studies of the fitness properties of various chromosomal inversions of *Drosophila* (Dobzhansky and Wallace, 1953). Because I can not find a better alternative, I use this terminology of coadaptation here to discuss the evolutionary process of selection for a balanced combination of *characters* in an

individual, and individuals in a population in the context of phenotypic evolution of quantitative characters.

Lande has made an attempt to use quantitative genetic concepts to discuss evolutionary phenomena of phenotypic adaptations between genetically correlated characters (Lande, 1979). He considered that genetic correlations between quantitative characters might be the basic cause of the phenotypic coadaptation of characters, as it is a well-known principle that the correlated response of a character Y to selection for a character X is proportional to the genetic correlation between characters X and Y. In his studies (Lande, 1979; Lande and Arnold, 1983), Lande analysed stabilizing and directional selection separately, and only for one cycle of selection in each case.

Many workers (including Lande) explicitly or implicitly hold the view that natural selection for adaptation is probably composed of two components —— one directive and the other stabilizing. So the process of adaptation and coadaptation of quantitative characters could be conceived as an interaction between stabilizing and directive components of natural selection. Following this view, I have shown in chapter 5 that the long-term correlated responses rely on the "coadaptive coefficients", the parameters of the fitness function of stabilizing selection. This suggests that the major cause of the coadaptation between quantitative characters in evolution might be the correlated stabilizing selection, not genetic correlations.

In chapter 5, I analysed stabilizing and directional selection in two steps, first stabilizing selection then directional selection, and used truncation as the form of directional selection. Alternatively, the fitness function could be assumed to be

$$w(x)=\exp\{\mathbf{a}^{T}x-(1/2)(x-\theta)^{T}W^{-1}(x-\theta)\} \qquad (6.1)$$

with the first term in the bracket of the right hand side of (6.1) approximating the forces of directional selection and the second approximating the forces of stabilizing selection, where $\mathbf{a}$ is the intensity vector of directional selection, θ is the optimum vector of stabilizing selection and W is the intensity matrix of stabilizing selection (see also (5.4) and (5.10)). This fitness function has been used quite frequently in the study of multivariate selection (*e.g.*, Felsenstein, 1977; Manly, 1981). It can be shown that with the assumption of (5.2) the mean vector after selection is

$$u^{*}=W(W+P)^{-1}[u+P(W^{-1}\theta+a)], \qquad (6.2)$$

from the relations

$$P^{*-1}=P^{-1}+W^{-1}$$

and $$P^{*-1}u^{*}=P^{-1}u+W^{-1}\theta+a$$

if W is positive definite (Felsenstein, 1977). Then if we follow the same argument as (5.12) to (5.18), we have from (6.2)

$$u_{\infty}=Wa_{\infty}+\theta, \qquad (6.3)$$

which is identical to (5.18) (in (5.18) $\theta=0$). So clearly in the long term the correlated responses are determined by the correlated influences of stabilizing selection (the matrix W) and not by genetic correlations, which is independent of the assumption of truncation.

The assumption of constancy of the optimum vector θ during the course of selection might be quite unrealistic. It might be expected

that, as the mean vector u moved, the optimum vector θ would tend to change. But the optimum vector θ would not be expected to change as quickly as the mean vector u. It has been shown in Fig.5.2 that only after a short time span (on an evolutionary time scale) the trajectory of the change of u would be along the major axes determined by the coadaptive coefficients, and such a pattern of change of u does not seem to rely on the constant values of θ.

Correlated selection determining the differentiation of populations on correlated characters has indeed been anticipated by some workers who have even described some general features of this process from logical reasoning and observation of nature (e.g., Simpson, 1953; Sokal, 1978). This study, however, provides a simple way to explain how this mechanism works, what kind of parameters are involved and how to test and prove it. However, although I have pointed out in chapter 5 that there is a connection between coadaptive coefficients and interpopulation correlations, this connection has not been worked out in detail yet. This would suggest the need for more analyses.

APPENDIX

From (3.18), (3.10) and (3.11), we have

$$f_\infty(z_i)=\frac{\mu_i \exp\{-(z_i-u_i)^2/(2m_i^2)\}}{(2\pi m_i^2)^{1/2}[1-\xi\exp\{-(z_i-B)^2/(2A)\}]}. \tag{A1}$$

$$(-\infty < z_i < \infty),$$

where ξ is a constant such that

$$\int_{-\infty}^{\infty} f_\infty(z_i)dz_i=1 \tag{A2}$$

and

$$u_i=\int_{-\infty}^{\infty} z_i f_\infty(z_i)dz_i. \tag{A3}$$

In this appendix, I prove $u_i=B$ in (A1).

First, we need to clarify the range of the constant ξ. Since (A1) is a density function and μ_i is a small value, this implies that

$$0 < 1-\xi\exp\{-(z_i-B)^2/(2A)\}$$

always, which suggests that $0 < \xi < 1$. Then it follows that

$$[1-\xi\exp\{-\frac{(z_i-B)^2}{2A}\}]^{-1}=\sum_{n=0}^{\infty}\xi^n\exp\{-\frac{n(z_i-B)^2}{2A}\}.$$

Therefore, (A1) can be written as

$$f_\infty(z_i)=\sum_{n=0}^{\infty}\mu_i\xi^n[\frac{A}{A+nm_i^2}]^{1/2}\exp\{-\frac{n(u_i-B)^2}{2(A+nm_i^2)}\}$$
$$[\frac{A+nm_i^2}{2\pi Am_i^2}]^{1/2}\exp\{-\frac{A+nm_i^2}{2Am_i^2}[z_i-\frac{u_i A+nm_i^2 B}{A+nm_i^2}]^2\}. \tag{A4}$$

after some calculation. Note that the last two terms in the right hand side of (A4) define a normal density function. By using this

property and putting (A4) into (A2) and (A3), we then obtain

$$\sum_{n=0}^{\infty} \mu_i \xi^n \left[\frac{A}{A+nm_i^2}\right]^{1/2} \exp\left\{-\frac{n(u_i-B)^2}{2(A+nm_i^2)}\right\} = 1$$

and $$\sum_{n=0}^{\infty} \mu_i \xi^n \left[\frac{A}{A+nm_i^2}\right]^{1/2} \exp\left\{-\frac{n(u_i-B)^2}{2(A+nm_i^2)}\right\} \frac{u_i A+nm_i^2 B}{A+nm_i^2} = u_i ,$$

or $$\sum_{n=0}^{\infty} \xi^n \left[\frac{A}{A+nm_i^2}\right]^{1/2} \exp\left\{-\frac{n(u_i-B)^2}{2(A+nm_i^2)}\right\} = \frac{1}{\mu_i} \qquad \text{(A5)}$$

and $$\sum_{n=0}^{\infty} \xi^n \left[\frac{A}{A+nm_i^2}\right]^{1/2} \exp\left\{-\frac{n(u_i-B)^2}{2(A+nm_i^2)}\right\} \frac{A+nm_i^2 B/u_i}{A+nm_i^2} = \frac{1}{\mu_i}. \qquad \text{(A6)}$$

Let $$a_n = \xi^n \left[\frac{A}{A+nm_i^2}\right]^{1/2} \exp\left\{-\frac{n(u_i-B)^2}{2(A+nm_i^2)}\right\}$$

and $$b_n = a_n \frac{A+nm_i^2 B/u_i}{A+nm_i^2}.$$

(A5) and (A6) are then equivalent to

$$\sum_{n=0}^{\infty} a_n = \sum_{n=0}^{\infty} b_n = \frac{1}{\mu_i}. \qquad \text{(A7)}$$

(i) Sufficiency:

It is easy to show that $\sum_{n=0}^{\infty} a_n$ is a monotonically decreasing series with positive terms. Then, if $u_i > B$, it follows that $a_n > b_n$ for $n = 1, 2, \ldots$, except $n=0$, where $a_0 = b_0$. Consequently, $\sum_{n=0}^{\infty} a_n > \sum_{n=0}^{\infty} b_n$ which contradicts the condition of (A7).

Similarly, if $u_i < B$, $\sum_{n=0}^{\infty} a_n < \sum_{n=0}^{\infty} b_n$ which also contradicts

the condition of (A7). While, then $u_i=B$, $a_n=b_n$ holds for every $n=0,1,2,\ldots$; therefore, (A7) is satisfied.

(ii) Necessity:

(A5) and (A6) can be rewritten as

$$\sum_{n=0}^{\infty} \xi^n \left[\frac{A}{A+nm_i^2}\right]^{1/2} \exp\left\{-\frac{n(u_i-B)^2}{2(A+nm_i^2)}\right\} = \sum_{n=0}^{\infty} \xi^n c_n \qquad \text{(A8)}$$

and $$\sum_{n=0}^{\infty} \xi^n \left[\frac{A}{A+nm_i^2}\right]^{1/2} \exp\left\{-\frac{n(u_i-B)^2}{2(A+nm_i^2)}\right\} \frac{A+nm_i^2 B/u_i}{A+nm_i^2} = \sum_{n=0}^{\infty} \xi^n d_n, \qquad \text{(A9)}$$

which are two power series. According to the identity theorem for power series, if the two power series

$$\sum_{n=0}^{\infty} \xi^n c_n \quad \text{and} \quad \sum_{n=0}^{\infty} \xi^n d_n$$

have the same sum in an interval $0 < \xi < 1$ (in this case) in which both of them converge, then the two series are entirely identical. That is to say, for every $n=0,1,2,\ldots$, $c_n=d_n$, since (A8) and (A9) do converge with $0 < \xi < 1$. It then gives $u_i=B$ always. Thus, the proof is completed.

GLOSSARY OF SYMBOLS

Some symbols with restricted use are not listed.

a	Effect of gene substitution in units of phenotypic standard deviation.
$\mathbf{a}$	Vector of directional selection forces.
$\mathbf{b}$	Vector of selection index coefficient.
c	Coefficient of centripetal selection (Latter's (1970) notation, $c=\omega^2(\omega^2+\sigma^2)^{-1}$).
E, e	Environmental deviations.
$\mathbf{E}$	Environmental covariance matrix.
$E( )$	Expectation.
$\mathbf{e}$	Vector of environmental deviations.
$f( ), g( ), h( )$	Density functions of distributions indicated by brackets.
$\mathbf{G}$	Genotypic covariance matrix.
$H( )$	Hermite polynomial.
h^2	Heritability ("narrow sense").
I	Selection index.
$\mathbf{I}$	Identity matrix.
k	Cumulant.
L	Selection limit.
m	Moment (Chs.3 and 4).
m	Number of characters in selection index (Ch.5).
m	As subscript, indicates mutation (Ch.4).
m^2	Variance of distribution of mutant effects.
n	Number of loci (Chs.3 and 4).

n	Number of characters (Ch.5).
p	Proportion selected by truncation.
$\mathbf{P}$	Phenotypic covariance matrix.
p	Gene frequency.
q	Gene frequency ($q=1-p$).
s	Selection differential.
t	Time in number of generations. As subscript or in bracket it means "at generation t".
u	Mean value of population indicated by subscript.
$\mathbf{u}$	Vector of population means indicated by subscript.
$\mathbf{W}$	Intensity matrix of stabilizing selection.
$\bar{W}$	Mean fitness of population.
$w(\ )$	Fitness function of selection.
X, x	Phenotypic values.
$\mathbf{x}$	Vector of phenotypic values.
Y, y	Genotypic values.
$\mathbf{y}$	Vector of genotypic values.
z	Standard deviation of truncation point τ.
z	Allelic effect.
α	Effect of newly arisen mutant in units of phenotypic standard deviation.
γ	Standardized cumulant (Ch.4).
γ	Coadaptive coefficient ($\gamma_{ij}=\omega_{ij}/\sqrt{(\omega_{ii}\omega_{jj})}$, Ch.5).
γ_1	Coefficient of skewness (Ch.3).
γ_2	Coefficient of kurtosis (Ch.3).
Δ	Indicates increment.

θ	Vector of optimum values in multidimentional stabilizing selection.
ι	Intensity of truncation selection; *i.e.*, selection differential in units of phenotypic standard deviation ($\iota=\varphi(Z)/P$).
λ	Rate of decay of variance from newly arisen mutants in subsequent generations.
μ	Mutation rate.
ϱ	Correlation between phenotype and genotype ($\varrho=h$).
Σ	Summation of the quantity following the sign.
σ or σ_i	Standard deviation (σ^2 or σ_{ii} = variance) of the quantity indicated by subscript.
σ_{ij}	Phenotypic covariance between character i and character j.
τ	Truncation point.
$\varphi(\ )$	Normal density function.
ω^2 or ω_{ii}, ω_{ij}	Intensity of stabilizing selection (components of matrix W).
$'$	As superscript, indicates after stabilizing selection but before truncation selection.
$*$	As superscript, indicates after truncation selection.

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